


ORIGINAL ARTICLE

Novel method to assess intrinsic heart rate recovery in ambulatory ECG recordings tracks cardioprotective effects of chronic autonomic regulation therapy in patients enrolled in the ANTHEM-HF study

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Background: Postexercise heart rate recovery (HRR) is a powerful and independent predictor of mortality. Autonomic regulation therapy (ART) with chronic vagus nerve stimulation (VNS) has been shown to improve ventricular function in patients with chronic heart failure. However, the effect of ART on HRR in patients with heart failure remains unknown.

Methods: A new measure involving quantification of intrinsic HRR was developed for 24-hr ambulatory ECG (AECG) recordings based on spontaneous heart rate changes observed during daily activity in patients with symptomatic heart failure and reduced ejection fraction. Intrinsic HRR values were compared in 21 patients enrolled in the ANTHEM-HF study (NCT01823887) before and after 12 months of chronic ART (10 Hz, 250 μ s pulse width, 18% duty cycle, maximum tolerable current amplitude after 10 weeks of titration) and to values from normal subjects (PhysioNet database, $n = 54$).

Results: With chronic ART, average intrinsic HRR was improved as indicated by a shortening of the rate-recovery time constant by 8.9% (from 12.3 ± 0.1 at baseline to 11.2 ± 0.1 s, $p < .0001$) among patients receiving high-intensity stimuli (≥ 2 mA). In addition, mean heart rate decreased by 8.5 bpm (from 75.9 ± 2.6 to 67.4 ± 2.9 bpm, $p = .005$) and left ventricular ejection fraction (LVEF) increased by 4.7% (from $32.6 \pm 2.0\%$ to $37.3 \pm 1.9\%$, $p < .005$).

Conclusion: Using a new technique adapted for 24-hr AECG recordings, intrinsic HRR was found to be impaired in patients with symptomatic HF compared to normal subjects. Chronic ART significantly improved intrinsic HRR, indicating an improvement in autonomic function.

KEYWORDS

autonomic reflexes, autonomic regulation therapy, baroreflex sensitivity, heart failure, heart rate recovery, vagus nerve stimulation

1 | INTRODUCTION

Although patients with heart failure benefit from widespread use of state-of-the-art drug treatments and implanted devices, their mortality and morbidity risk remains high (Joffe et al., 2013). Abnormally high sympathetic nervous system activity combined with lower than normal parasympathetic activation characterizes autonomic dysfunction observed in heart failure, (Brunner-La Rocca, Jennings, & Kaye, 2001) as the autonomic nervous system responds to a cardiac insult by up-regulating sympathetic activity while withdrawing parasympathetic activity. Treatment to reverse this abnormal condition by the use of chronic peripheral vagus nerve stimulation has received considerable attention (Ardell et al., 2016; De Ferrari, 2014).

Autonomic regulation therapy (ART) via chronic vagus nerve stimulation (VNS) has been shown to modulate autonomic mechanisms that reduced heart failure symptom expression, enhance objective measures of ventricular structure and performance, (De Ferrari et al., 2011; Premchand et al., 2014, 2015) and favorably alter markers of risk for fatal arrhythmias, including heart rate turbulence and T-wave alternans (TWA), indicators of cardiovascular mortality and sudden cardiac death risk (Verrier et al., 2011; Bauer et al., 2008). Several clinical studies have demonstrated the beneficial effects of VNS in patients with heart failure, including but not limited to a significant improvement in left ventricular ejection fraction (LVEF), left ventricular end-systolic volume (LVESV), New York Heart Association (NYHA) class, (De Ferrari et al., 2011; Premchand et al., 2014, 2015) and autonomic balance by heart rate variability (Libbus, Nearing, Amurthur, KenKnight, & Verrier, 2016). VNS has a proven safety profile with low incidence of side effects and adverse events in the management of more than 100,000 patients with epilepsy or depression, (Conway, Colijn, & Schachter, 2015) and therefore promises to provide a reasonable device-based solution for treatment of symptomatic heart failure in the presence of guideline-directed medical therapy.

Because ART via chronic VNS has been shown to improve autonomic balance and ventricular structure and function in patients with heart failure, automated analysis of a patient's autonomic function may be a valuable tool for periodically assessing progression of heart failure and the effect of chronic VNS. Exercise-based heart rate recovery (HRR) has been shown to be a powerful and independent predictor of cardiovascular mortality, (Watanabe, Thamarasan, Blackstone, Thomas, & Lauer, 2001; Nishime, Cole, Blackstone, Pashkow, & Lauer, 2000; Tang, Dewland, Wencker, & Katz, 2009) morbidity, (Tang et al., 2009; Sheppard et al., 2007), and sudden cardiac death, (Jouven et al., 2005) as it reflects impaired parasympathetic nerve activity and lessened capacity to withdraw sympathetic activity as influenced by baroreceptor gain. It is suitable for risk stratification of patients with heart failure (Nanas et al., 2006). However, changes in intrinsic HRR in response to chronic VNS have not been investigated.

Patients with chronic heart failure exhibit abnormal HRR (typically ≤ 12 bpm), assessed upon completion of a controlled exercise protocol (Cole, Blackstone, Pashkow, Snader, & Lauer, 1999). However, in many

cases, the health of patients with heart failure is so impaired that they lack the physical ability to perform, let alone complete, the specified exercise protocol. In these cases, an accurate measure of postexercise HRR cannot be obtained. Furthermore, since HRR is measured following only one instance of provoked heart rate increase in a patient, it may not accurately represent the patient's autonomic function at different times of day.

To circumvent the need to subject patients with advanced heart failure to repeated episodes of exercise testing and to obtain an estimate of autonomic function at multiple time points throughout the day and night, we developed an algorithm for determining HRR using spontaneous heart rate changes that occur during daily activities. We defined this parameter as the intrinsic HRR to reflect its capacity to measure the autonomic response to periods of naturally occurring surges in heart rate.

We hypothesized that intrinsic HRR would decrease in response to ART with chronic VNS in patients with heart failure, reflecting an improvement in overall autonomic regulation of heart rate. Ambulatory ECG (AECG) 24-hr recordings from patients with chronic, symptomatic heart failure and reduced LVEF who were enrolled in the Autonomic Neural Regulation Therapy to Enhance Myocardial Function in Heart Failure (ANTHEM-HF) study (NCT01823887) were analyzed to compare the intrinsic HRR values prior to and after chronic VNS therapy to evaluate whether chronic ART improves autonomic function in this patient population.

2 | METHODS

2.1 | Patient data and characteristics

The study design and patient selection criteria of the ANTHEM-HF study have been previously described (Premchand et al., 2014). 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, subjects with NYHA functional class II/III heart failure and age ≥ 18 years were enrolled at 10 sites. Inclusion criteria included LVEF $\leq 40\%$, left ventricular end-diastolic dimension ≥ 50 and < 80 mm, QRS width ≤ 150 ms, and optimal medical management, including stable beta-blocker therapy for heart failure as indicated and tolerated for at least 3 months and all other oral pharmacologic therapy for heart failure, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, loop diuretics, and spironolactone, for at least 1 month. Patients were also required to be capable of performing the 6-min walk test (6MWT) with a baseline distance of 150–425 m, limited by heart failure symptoms.

Enrolled patients were implanted with a vagus nerve stimulation system (Cyberonics, Inc., Houston, TX, USA) on either the left or right cervical vagus nerve and stimulation was titrated to maximum tolerable current amplitude over 10 weeks. Chronic cyclic stimulation was applied for 12 months at a frequency of 10 Hz, a pulse width of 250 μ s, and a duty cycle of 14 s on/66 s off. Continuous cyclic stimulation at low-intensity (< 2 mA; $n = 8$) or high-intensity (≥ 2 mA; $n = 13$)

levels was maintained as tolerated throughout the titration period and the 12-month follow-up period.

AECG recordings (Digitrak XT, Philips Medical Systems, Best, The Netherlands) were made at baseline and after 6 and 12 months of chronic therapy. All patients enrolled in ANTHEM-HF whose AECG files could be extracted and were available for analysis at baseline and 12 months were included ($n = 25$). Four patients had excessive premature ventricular contractions (PVCs) that prevented analysis; the remaining 21 patients were included in the present analysis.

Data from 54 normal subjects (30 men, age 28.5–76; 24 women, age 28–73) were obtained from a publically available database of long-term AECG recordings (PhysioNet Normal Sinus Rhythm [NSR] database).

2.2 | Intrinsic heart rate recovery analysis

Intrinsic HRR was calculated as the slope in seconds of the gradual decrease in heart rate following a spontaneous heart rate surge such as often occurs in connection with activities of daily living including, but not limited to, postural changes, (McCrary et al., 2016) emotions, and physical exertion.

Intrinsic HRR exhibits some degree of nonlinearity as the amplitude of the perturbation affects the relaxation time constant. To quantify intrinsic HRR, we modeled heart rate deceleration as a mono-exponential decay at multiple time points before, during, and after recovery and estimated the time constant (T_R) of heart rate decay. The equation of the trend line for this decay is:

$$HR(t) = a_0 + b \cdot e^{(-1/TR) \cdot t}$$

In this equation, a_0 is the asymptotic value of the heart rate, b is the decremented value below the peak heart rate, and T_R is the time constant, which reflects HRR such that a smaller time constant reflects a faster HRR response.

The maximum HRR value is reported for each 24-hr AECG recording. Figure 1 illustrates a method of extracting intrinsic HRR. The x-axis represents a portion of the 24-hr monitoring period and the y-axis represents the patient's heart rate. Instantaneous heart rate measurements were smoothed to remove isolated spikes in heart rate changes. Heart rate smoothing was calculated with a 5-beat moving median followed by a 5-beat moving mean. From the smoothed heart rate data, paired local maxima and local minima were identified and were analyzed to determine the candidate HRR events in the heart rate stream for each 24-hr AECG record.

In Figure 1, a sequence of paired maxima points and minima points were analyzed to identify a minimum decrease in heart rate of at least 5 bpm and a maximum heart rate increase of 30 bpm between the initial maximum heart rate (HR_0) and the final heart rate (HR_{asym}). In this representative example, the decrease in heart rate is represented by the set of points comprising the initial maximum (HR_0), four subsequent maxima points, and four subsequent minima points. The initial maximum point (HR_0) was the beginning of this candidate region of interest.

Once the initial heart rate maximum point was identified, subsequent maxima points and minima points were analyzed to determine whether two criteria were satisfied: first, that each maximum point is less than the immediately preceding maximum point; and second, that each minimum point is less than HR_0 and the immediately preceding minimum point. In this example, each of the four subsequent maxima points is less than the immediately preceding maximum point, and each of the four subsequent minima points is less than HR_0 and the immediately preceding minimum point. This beat stream exhibits a gradually decreasing heart rate indicative of the patient's HRR. Finally, the heart rate reaches the 5th minimum point, which is greater than the immediately preceding minimum point. This change fails the second criterion and therefore establishes the end of the region of interest shown in Figure 1. The preceding criteria were applied to all subsequent candidate HR_0 maxima to the end of the recorded heart rate sequence.

It is desirable to extract only those candidate events that include at least three maxima-minima pairs. As shown in Figure 1, a candidate event that includes four maxima-minima pairs was identified as an intrinsic HRR event of interest. Candidate events having <3 maxima-minima pairs cannot model exponential decay and would not provide meaningful insight into the patient's intrinsic HRR. It is also desirable for the candidate event to occur over no more than a maximum period of time. Candidate events in which the estimated time constant (T_R) exceeded 1 min were excluded. All candidate events were captured for the entire AECG record using the above algorithm to scan and validate all sequences of maxima and minima from the beginning to the end of the recordings.

After all intrinsic HRR events in the dataset were identified, a first-order exponential (as described above) was taken of each identified intrinsic HRR event in the heart rate dataset to produce a modeled time constant (T_R) and a corresponding modeled change in heart rate (ΔHR) from the first maximum and the subsequent minima. The calculated time constant for the intrinsic HRR event was identified as the relaxation parameter T_R for that intrinsic HRR event.

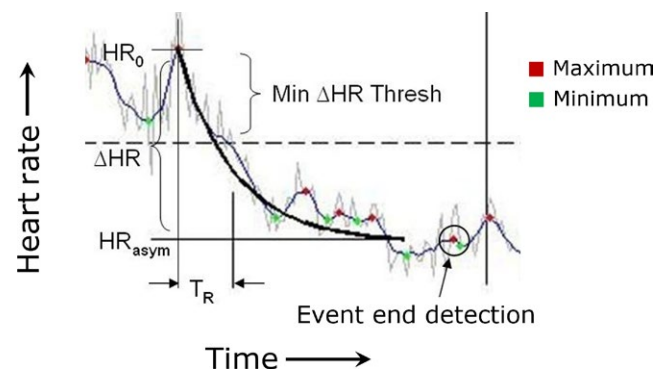


FIGURE 1 Method for calculating intrinsic heart rate recovery (HRR) from spontaneous heart rate changes in ambulatory electrocardiograms (AECGs) recorded during daily activity. An initial heart rate maximum point (HR_0) is identified and subsequent HRR to the final heart rate (HR_{asym}) is fit to a mono-exponential decay with time constant of recovery (T_R), based on a sequence of smoothed and decaying heart rate maxima and minima

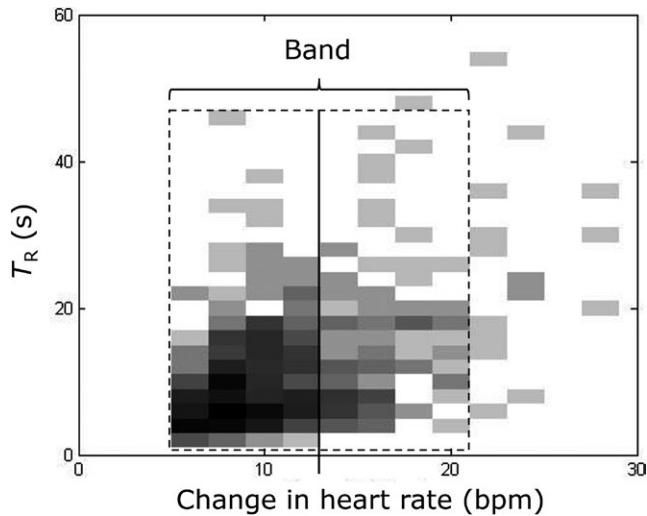


FIGURE 2 Gray-level intrinsic heart rate recovery (HRR) histogram of time constant of recovery (T_R), showing the distribution of heart rate-dependent intrinsic HRR for all qualified intrinsic HRR events for a sample subject. The mean banded relaxation parameter is calculated for each change in heart rate in 1-bpm increments

Data from one patient for one follow-up recording are presented as a histogram of the intrinsic HRR events identified over a 24-hr period of time where the modeled relaxation parameter (T_R) was plotted on the y-axis against the corresponding change in heart rate (ΔHR) for all events (Figure 2). Next, the mean banded relaxation parameter, the average relaxation parameter within a heart rate window, was calculated for each heart rate change. In order to include sufficient data points for each heart rate change level, the mean was taken of the relaxation parameters in a band (± 8 bpm) around each heart rate change level. The center of the band was moved in 1-bpm steps from 13 to 22 bpm. An example heart rate change level is identified by a solid vertical line. More than 2000 detectable events were analyzed from each 24-hr Holter record.

2.3 | Statistical methods

Effects of VNS on intrinsic HRR and other parameters were analyzed with paired *t*-tests. Data are reported as mean \pm SEM. $p < .05$ was considered statistically significant.

3 | RESULTS

Baseline characteristics of the 21 ANTHEM-HF patients included in the HRR analysis are summarized in Table 1. None had an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) device. The baseline characteristics were similar for patients implanted on the left or right side.

Intrinsic HRR increased as a function of change in heart rate both for normal subjects and for patients with heart failure (Figure 3). At baseline, patients had a significantly prolonged intrinsic HRR (from 9.8 ± 0.08 to 13.5 ± 0.26 s) as compared to normal subjects (from

7.8 ± 0.04 to 10.4 ± 0.09 s, $p < .005$). Intrinsic HRR was improved as indicated by a shortening of the rate-recovery time constant by 8.9% (from 12.3 ± 0.1 s at baseline to 11.2 ± 0.1 s, $p < .0001$; Table 2) after 12 months of chronic ART in patients who received high-intensity stimuli (≥ 2 mA), suggesting improvement in parasympathetic activity and autonomic nervous system regulation of heart rate. Patients receiving low-intensity stimuli (< 2 mA) did not experience reduced intrinsic HRR.

LVEF and heart rate were also significantly improved at 12 months, suggesting improved autonomic status (Table 2). LVEF increased by 4.7% ($p < .005$) in patients with high-intensity stimulation and by 2.9% ($p = .16$) in patients with low-intensity stimulation. Average daily heart rate was reduced by 8.5 bpm ($p = .005$) in patients with high-intensity stimulation and by 10.4 bpm ($p = .015$) in patients with low-intensity stimulation.

4 | DISCUSSION

A new method was developed that permits assessment of intrinsic HRR in AECG recordings. This technique has advantages over conventional postexercise HRR as it does not require an exercise test, which may not be possible in subjects with advanced disease, including heart failure and age-related physical disabilities. Also, this novel approach is capable of monitoring multiple events such as exertion, mental stress, and postural changes (Nanas et al., 2006) as compared to a single postexercise test. The technique provides a robust assessment of autonomic control, as more than 2000 detectable events were analyzed from each 24-hr Holter recording, ranging from over 400 events at 13 bpm to over 75 events at 22 bpm. Intrinsic HRR revealed significant abnormalities in patients with impaired left ventricular function enrolled in the ANTHEM-HF study compared to normal subjects. We further demonstrated that chronic VNS significantly improved intrinsic HRR as well as heart rate after 12 months of therapy. It is of interest that in patients with angiographically demonstrated CAD following exercise rehabilitation, Kentta and coworkers (Kentta et al., 2014) demonstrated a parallel improvement in postexercise HRR and TWA, which was presumably mediated by increased vagal tone secondary to augmentation of baroreflex sensitivity.

4.1 | Prior studies of cardioprotective mechanisms of vagus nerve stimulation

It has been previously shown that VNS can have a protective benefit to the heart in the setting of heart failure, (De Ferrari et al., 2011) likely due in large extent by augmenting parasympathetic activity. Circulating cytokine levels are elevated in patients with heart failure, (Deswal et al., 2001) and it has been observed that VNS can reduce circulating cytokine levels in a preclinical model of reduced ejection fraction heart failure (Sabbah et al., 2011). In addition, VNS inhibits neural release of norepinephrine at cardiac effectors, (Kawada et al., 2006) restores autonomic balance as reflected in improvements in heart rate variability and baroreflex sensitivity, (De Ferrari et al., 2011;

TABLE 1 Patient characteristics at enrollment

Demographics	Left (n = 11)	Right (n = 10)	Overall (n = 21)
Age (year)	46.8 ± 3.7	45.6 ± 3.3	46.2 ± 2.4
Male, n (%)	10 (91)	7 (70)	17 (81)
Medical history			
Duration of heart failure (year)	4.2 ± 1.2	3.1 ± 1.1	3.7 ± 0.8
Heart failure etiology (%)			
Ischemic n (%)	8 (73)	7 (70)	15 (71)
Nonischemic n (%)	3 (27)	3 (30)	6 (29)
Clinical examination			
NYHA II/III, n (%)	7 (64)/4 (36)	6 (60)/4 (40)	13 (62)/8 (38)
MLHFQ score	40.0 ± 4.3	45.1 ± 2.7	42.4 ± 2.6
Body mass index (kg/m ²)	23.1 ± 1.0	24.5 ± 1.3	23.8 ± 0.8
LVEF (%)	33.6 ± 2.2	31.4 ± 2.2	32.5 ± 1.5
LVESV (ml)	103.6 ± 10.6	101.8 ± 8.5	102.7 ± 6.7
LVESD (mm)	50.4 ± 2.0	52.3 ± 1.5	51.3 ± 1.3
LVEDV (ml)	154.0 ± 12.5	147.5 ± 10.9	150.9 ± 8.2
LVEDD (mm)	60.9 ± 1.8	62.2 ± 1.3	61.5 ± 1.1
Heart rate (bpm)	75 ± 2	79 ± 4	77 ± 2
Systolic BP (mmHg)	110 ± 5	102 ± 4	106 ± 3
Diastolic BP (mmHg)	75 ± 3	69 ± 3	72 ± 2
6MWT (m)	320 ± 7	287 ± 26	304 ± 13
QRS width (ms)	111 ± 7	108 ± 8	110 ± 5

6MWT, 6 min walk test; BP, blood pressure; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, Left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; MLHFQ, Minnesota Living with Heart Failure questionnaire; NYHA, New York Heart Association.

TABLE 2 Changes in LVEF, heart rate, and intrinsic heart rate recovery from baseline to 12 months of therapy in patients with low-intensity stimuli (<2 mA) (n = 8) and high-intensity stimuli (≥2 mA) (n = 13)

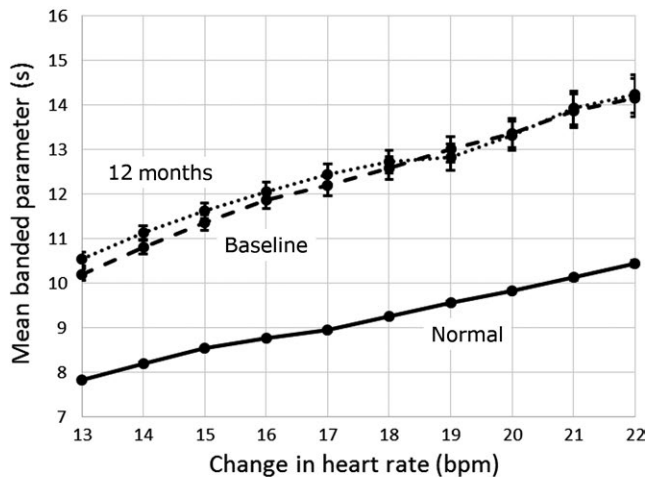
Measurement	Baseline	12 months	Change	p-value
LVEF (%) in patients with low-intensity stimuli	32.4 ± 2.5	35.2 ± 2.4	2.9	.16
LVEF (%) in patients with high-intensity stimuli	32.6 ± 2.0	37.3 ± 1.9	4.7	<.005
Heart rate (bpm) in patients with low-intensity stimuli	78.8 ± 3.5	68.4 ± 2.7	-10.4	.015
Heart rate (bpm) in patients with high-intensity stimuli	75.9 ± 2.6	67.4 ± 2.9	-8.5	.005
Intrinsic HRR (s) in patients with low-intensity stimuli	13.0 ± 1.0	13.1 ± 0.1	+0.1	.63
Intrinsic HRR (s) in patients with high-intensity stimuli	12.3 ± 0.1	11.2 ± 0.1	-1.1	<.0001

HRR, heart rate recovery; LVEF, left ventricular ejection fraction.

Zhang et al., 2009) reduces systemic inflammation, (Pavlov, Wang, Czura, Friedman, & Tracey, 2003) increases coronary flow, (Henning & Sawmiller, 2001) and exerts antiapoptotic effects (Uemura et al., 2007; Beaumont et al., 2015). These beneficial effects provide putative mechanistic bases for clinical improvements that have been observed in cardiac function and reduction in heart failure symptoms (De Ferrari et al., 2011; Premchand et al., 2014, 2015).

However, despite encouraging evidence from these preclinical and clinical studies, the recently completed INOVATE-HF trial found that chronic right-sided VNS using the CardioFit system (BioControl, Yehud, Israel), while meeting its safety endpoints, did not reduce all-cause mortality or heart failure events in the cohort investigated (Gold et al., 2016). The failure of the INOVATE-HF study to meet its primary efficacy endpoints was likely due to the inclusion of a significant number

Low-intensity stimulation



High-intensity stimulation

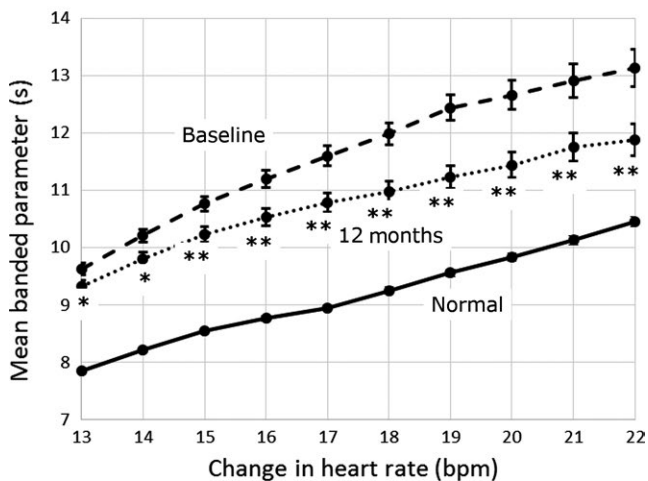


FIGURE 3 Intrinsic heart rate recovery (HRR) (y-axis) as a function of heart rate change (x-axis) for normal subjects (solid line) and in patients with heart failure at baseline (dashed line) and after 12 months of chronic autonomic regulation therapy (ART) (dotted line). Patients with low-intensity stimulation (upper panel) showed no change in intrinsic HRR. Patients with high-intensity stimulation (lower panel) showed a significant improvement in intrinsic HRR at every change in heart rate (* $p < .05$; ** $p < .005$)

of patients with CRT devices and persistent heart failure symptoms, as well as the use of a stimulation frequency that was too low and a VNS active phase (mean ON-time of only 5 s) that was insufficient to elicit therapeutic benefits (Gold et al., 2016; Byku & Mann, 2016).

4.2 | This study

The present investigation is a secondary subanalysis of the ANTHEM-HF patient cohort, which had an LVEF of $32.4 \pm 7.2\%$. None of the patients had ICD or CRT devices and no intracardiac catheter was used in connection with VNS delivery. VNS was performed on either right or left side using an electrode system proven to be safe

and effective in >100,000 patients treated for epilepsy or depression (Conway et al., 2015).

The novel HRR method developed in this study provides insights into two aspects relevant to heart failure and the potential for neurostimulation therapy. First, we demonstrated using a unique AECG-based method for HRR quantification that patients with heart failure showed poor HRR during daily activities compared to normal subjects (Figure 3). This observation is consistent with the findings obtained using a conventional approach of measuring HRR in the few seconds or minutes following cessation of a standardized exercise test (Imai et al., 1994). A sizeable body of evidence suggests that impaired HRR relates to reduced baroreflex sensitivity, which in turn blunts the vagally mediated postexercise heart rate slowing (Coote, 2010; Lauer, 2016). In a prior secondary subanalysis of ANTHEM-HF patients, (Libbus et al., 2016) we found abnormally low baseline high-frequency HRV indicating depression in parasympathetic activity, which is consistent with impairment of intrinsic HRR observed in this study. Thus, the results of quantitatively assessed intrinsic HRR in AECG recordings concur with those obtained following exercise and may be conceptually related to baroreflex sensitivity.

The second major discovery of this study is that intrinsic HRR measurement may be used to track the effects of chronic VNS therapy on autonomic function. After 12 months of VNS, there was a significant 8.9% improvement in intrinsic HRR in patients receiving high-intensity stimulation. Because baroreceptors are a major control point, (Lauer, 2016) the net effect on cardiac function through the multifold cardioprotective influence of chronic vagal activation (e.g., antisymphetic, anti-inflammatory, antiapoptotic, and anti-eNOS activation) may be substantial. In fact, indices of cardiac function such as LVEF and NYHA Class were significantly improved by chronic VNS in ANTHEM-HF patients (Premchand et al., 2014, 2015). Also reported in ANTHEM-HF patients, (Libbus et al., 2016) VNS improved high-frequency HRV and rMSSD HRV, both reflecting parasympathetic activity, as well as HRT slope, and lowered heart rate. These changes were accompanied by decreased TWA and occurrence of VT (Libbus et al., 2016).

Reduction in resting heart rate has been shown to be a major determinant of clinical benefit in pharmacological studies. The significant VNS-induced reduction in heart rate (by 8 bpm , from 78 ± 11 to $70 \pm 10 \text{ bpm}$), previously reported in ANTHEM-HF patients (Premchand et al., 2014) was greater than the 6-bpm decrease reported for ivabradine in the BEAUTIFUL trial (Fox et al., 2008). This trial demonstrated that ivabradine reduced risk for cardiovascular death, hospital admissions for heart failure or myocardial infarction, and coronary revascularization among patients with CAD and left ventricular systolic dysfunction and baseline 24-hr mean heart rates $>70 \text{ bpm}$. The physiological bases for the cardioprotective effects of reduced heart rate have been discussed in detail (Verrier & Tan, 2009).

A potential further application of intrinsic HRR is to determine the therapeutic efficacy of ART. Observed changes in the patient's intrinsic HRR may be used to optimize therapy by enabling the clinician to adjust stimulation parameters until the maximum intrinsic HRR improvement is achieved.

4.3 | Limitations

This study introduces the concept of intrinsic HRR, a parameter that can be derived using spontaneous heart rate changes observed during daily activities on AECG recordings. However, intrinsic HRR has not been compared with HRR measurements made in conjunction with exercise protocols. Furthermore, a limited number of the paired AECG records were available for analysis from the overall ANTHEM-HF cohort. Intrinsic HRR should be evaluated in a larger population of patients in a randomized, controlled clinical setting to better clarify its role in the management of heart failure. In future cohorts, there may be a need for some adjustment in thresholds for prediction of outcomes.

5 | CONCLUSION

Utilizing a new analytical method applied to 24-hr AECG recordings, intrinsic HRR was found to be depressed in patients with symptomatic HF compared to normal subjects, as indicated by prolonged time constants of rate recovery. High-intensity chronic ART significantly enhanced intrinsic HRR after 12 months, demonstrated by a shortening of rate-recovery time constants, indicating an improvement in autonomic function.

DISCLOSURES

This study was funded by LivaNova. Drs. Carlson, Libbus, KenKnight, and Mr. Amurthur are employees of LivaNova. Dr. Verrier discloses no conflicts of interest.

REFERENCES

Ardell, J. L., Andresen, M. C., Armour, J. A., Billman, G. E., Chen, P. S., Foreman, R. D., ... Zucker, I. H. (2016). Translational neurocardiology: Preclinical models and cardioneural integrative aspects. *Journal of Physiology*, 594, 3877–3909.

Bauer, A., Malik, M., Schmidt, G., Barthel, P., Bonnemeier, H., Cygankiewicz, I., ... Zareba, W. (2008). Heart rate turbulence: Standards of measurement, physiological interpretation, and clinical use: international Society for Holter and Noninvasive Electrophysiology Consensus. *Journal of the American College of Cardiology*, 52, 1353–1365.

Beaumont, E., Southerland, E. M., Hardwick, J. C., Wright, G. L., Ryan, S., Li, Y., ... Ardell, J. L. (2015). Vagus nerve stimulation mitigates intrinsic cardiac neuronal and adverse myocyte remodeling post myocardial infarction. *American Journal of Physiology*, 309, H1198–H1206.

Brunner-La Rocca, H. P. E. M., Jennings, G. L., & Kaye, D. M. (2001). Effects of cardiac sympathetic nervous activity on mode of death in congestive heart failure. *European Heart Journal*, 22, 1136–1143.

Byku, M., & Mann, D. L. (2016). Neuromodulation of the failing heart: Lost in translation? *JACC*, 1, 95–106.

Cole, C. R., Blackstone, E. H., Pashkow, F. J., Snader, C. E., & Lauer, M. S. (1999). Heart-rate recovery immediately after exercise as a predictor of mortality. *NEJM*, 341, 1351–1357.

Conway, C. R., Colijn, M. A., & Schachter, S. C. (2015). Vagus nerve stimulation for epilepsy and depression. In Reti, I. M. (ed.), *Brain Stimulation*, Hoboken, NJ: John Wiley & Sons, 305–335.

Coote, J. H. (2010). Recovery of heart rate following intense dynamic exercise. *Experimental Physiology*, 95, 431–440.

De Ferrari, G. M. (2014). Vagal stimulation in heart failure. *Journal of Cardiovascular Translational Research*, 7, 310–320.

De Ferrari, G. M., Crijns, H. J. G. M., Borggrefe, M., Milasinovic, G., Smid, J., Zabel, M., ... Schwartz, P. J. (2011). Chronic vagus nerve stimulation: A new and promising therapeutic approach for chronic heart failure. *European Heart Journal*, 32, 847–855.

Deswal, A., Petersen, N. J., Feldman, A. M., Young, J. B., White, B. G., & Mann, D. L. (2001). Cytokines and cytokine receptors in advanced heart failure: An analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation*, 103, 2055–2059.

Fox, K., Ford, I., Steg, P. G., Tendera, M., Robertson, M., & Ferrari, R. (2008). Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A subgroup analysis of a randomised controlled trial. *Lancet*, 372, 817–821.

Gold, M. R., Van Veldhuisen, D. J., Hauptman, P. J., Borggrefe, M., Kubo, S. H., Lieberman, R. A., ... Mann, D. L. (2016). Vagus nerve stimulation for the treatment of heart failure: The INOVATE-HF trial. *Journal of the American College of Cardiology*, 68, 149–158.

Henning, R. J., & Sawmiller, D. R. (2001). Vasoactive intestinal peptide: Cardiovascular effects. *Cardiovascular Research*, 49, 27–37.

Imai, K., Sato, H., Hori, M., Kusuoka, H., Ozaki, H., Yokoyama, H., ... Kamada, T. (1994). Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. *Journal of the American College of Cardiology*, 24, 1529–1535.

Joffe, S. W., Webster, K., McManus, D. D., Kiernan, M. S., Lessard, D., Yarzebski, J., ... Goldberg, R. J. (2013). Improved survival after heart failure: A community-based perspective. *Journal of the American Heart Association*, 2, e000053.

Jouven, X., Empana, J. P., Schwartz, P. J., Desnos, M., Courbon, D., & Ducimetiere, P. (2005). Heart-rate profile during exercise as a predictor of sudden death. *NEJM*, 352, 1951–1958.

Kawada, T., Yamazaki, T., Akiyama, T., Li, M., Ariumi, H., Mori, H., ... Sugimachi, M. (2006). Vagal stimulation suppresses ischemia-induced myocardial interstitial norepinephrine release. *Life Sciences*, 78, 882–887.

Kentta, T., Tulppo, M. P., Nearing, B. D., Karjalainen, J. J., Hautala, A. J., Kiviniemi, A. M., ... Verrier, R. L. (2014). Effects of exercise rehabilitation on cardiac electrical instability assessed by T-wave alternans during ambulatory electrocardiogram monitoring in coronary artery disease patients without and with diabetes mellitus. *American Journal of Cardiology*, 114, 832–837.

Lauer, M. S. (2016). Heart rate recovery: Coming back full-circle to the baroreceptor reflex. *Circulation Research*, 119, 582–583.

Libbus, I., Nearing, B. D., Amurthur, B., KenKnight, B. H., & Verrier, R. L. (2016). Autonomic regulation therapy suppresses quantitative T-wave alternans and improves baroreflex sensitivity in patients with heart failure enrolled in the ANTHEM-HF study. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 13, 721–728.

McCrorry, C., Berkman, L. F., Nolan, H., O'Leary, N., Foley, M., & Kenny, R. A. (2016). Speed of heart rate recovery in response to orthostatic challenge. *Circulation Research*, 119, 666–675.

Nanas, S., Anastasiou-Nana, M., Dimopoulos, S., Sakellariou, D., Alexopoulos, G., Kapsimalakou, S., ... Nanas, J. (2006). Early heart rate recovery after exercise predicts mortality in patients with chronic heart failure. *International Journal of Cardiology*, 110, 393–400.

Nishime, E. O., Cole, C. R., Blackstone, E. H., Pashkow, F. J., & Lauer, M. S. (2000). Heart rate recovery and treadmill exercise score as predictors of mortality in patients referred for exercise ECG. *JAMA*, 284, 1392–1398.

Pavlov, V. A., Wang, H., Czura, C. J., Friedman, S. G., & Tracey, K. J. (2003). The cholinergic anti-inflammatory pathway: A missing link in neuroimmunomodulation. *Molecular Medicine*, 9, 125–134.

Premchand, R. K., Sharma, K., Mittal, S., Monteiro, R., Dixit, S., Libbus, I., ... Anand, I. S. (2014). Autonomic regulation therapy via left or right

- cervical vagus nerve stimulation in patients with chronic heart failure: Results of the ANTHEM-HF trial. *Journal of Cardiac Failure*, 20, 808–816.
- Premchand, R. K., Sharma, K., Mittal, S., Monteiro, R., Libbus, I., DiCarlo, L., ... Anand, I. S. (2015). ENCORE: Extension of the ANTHEM-HF study evaluating autonomic regulation therapy in reduced ejection fraction heart failure. *Journal of Cardiac Failure*, 21, 940.
- Sabbah, H. N., Ilsar, I., Zaretsky, A., Rastogi, S., Wang, M., & Gupta, R. C. (2011). Vagus nerve stimulation in experimental heart failure. *Heart Failure Reviews*, 16, 171–178.
- Sheppard, R. J., Racine, N., Roof, A., Ducharme, A., Blanchet, M., & White, M. (2007). Heart rate recovery—a potential marker of clinical outcomes in heart failure patients receiving beta-blocker therapy. *Canadian Journal of Cardiology*, 23, 1135–1138.
- Tang, Y. D., Dewland, T. A., Wencker, D., & Katz, S. D. (2009). Post-exercise heart rate recovery independently predicts mortality risk in patients with chronic heart failure. *Journal of Cardiac Failure*, 15, 850–855.
- Uemura, K., Li, M., Tsutsumi, T., Yamazaki, T., Kawada, T., Kamiya, A., ... Sugimachi, M. (2007). Efferent vagal nerve stimulation induces tissue inhibitor of metalloproteinase-1 in myocardial ischemia-reperfusion injury in rabbit. *American Journal of Physiology*, 293, H2254–H2261.
- Verrier, R. L., Klingenhoben, T., Malik, M., El-Sherif, N., Exner, D. V., Hohnloser, S. H., ... Rosenbaum, D. S. (2011). Microvolt T-wave alternans physiological basis, methods of measurement, and clinical utility—consensus guideline by International Society for Holter and Noninvasive Electrocardiology. *Journal of the American College of Cardiology*, 58, 1309–1324.
- Verrier, R. L., & Tan, A. (2009). Heart rate, autonomic markers, and cardiac mortality. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 6, S68–S75.
- Watanabe, J., Thamilarasan, M., Blackstone, E. H., Thomas, J. D., & Lauer, M. S. (2001). Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: The case of stress echocardiography. *Circulation*, 104, 1911–1916.
- Zhang, Y., Popovic, Z. B., Bibevski, S., Fakhry, I., Sica, D. A., Van Wagoner, D. R., ... Mazgalev, T. N. (2009). Chronic vagus nerve stimulation improves autonomic control and attenuates systemic inflammation and heart failure progression in a canine high-rate pacing model. *Circulation: Heart Failure*, 2, 692–699.

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