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Baseline NT-proBNP and responsiveness to autonomic regulation therapy in patients with heart failure and reduced ejection fraction

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ABSTRACT

Background: Recent heart failure studies have associated lower baseline natriuretic peptide levels with improved morbidity/mortality outcomes during pharmaceutical treatment, and better clinical outcomes during neuromodulation (NM) with carotid nerve plexus stimulation for HFrEF when NT-proBNP < 1600 pg/ml. Whether baseline NT-proBNP is associated with HFrEF responsiveness to NM using vagus nerve stimulation (VNS) has not been examined. Hence, we evaluated the interaction of baseline NT-proBNP with changes in symptoms and function that occurred during chronic VNS in the ANTHEM-HF study.
Methods: A repeated measures, generalized-estimating, equations model evaluated the relationship of baseline NT-proBNP values above and below 1600 pg/ml to symptomatic and functional responses in ANTHEM-HF.
Results: Median (interquartile range; maximum) NT-proBNP was 868 (322, 1875; 14,656) pg/ml (N = 58). Heart rate (HR), HR variability (SDNN), 6-minute walk distance, MLWHF mean score, and NYHA improved significantly, independent of baseline NT-proBNP. While there was a statistical interaction between baseline NT-proBNP and better LVEF improvement during VNS, LVEF improved overall in the study cohort (N = 60; 32 ± 7 to 37 ± 10%; p = 0.0042), and in those patients whose baseline NT-proBNP was below the median baseline NT-proBNP value (n = 29; 36 ± 6 to 42 ± 10%; p < 0.0025)] or above this value (n = 29; 29 ± 7 to 32 ± 9%; p < 0.05).
Conclusions: In ANTHEM-HF, overall symptomatic and functional improvement during chronic VNS was independent of baseline NTproBNP. These are preliminary and hypothesis-generating findings, and the reason for a differing interaction between baseline NT-proBNP and response to CNPS and VNS remains unclear. It is anticipated that the ongoing ANTHEM-HFrEF Pivotal Study of VNS will provide additional insight.

1. Introduction

Recent trials have reported that lower baseline levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels are associated with improved morbidity/mortality outcomes during pharmacologic treatment of patients with heart failure and preserved left ventricular ejection fraction (HFpEF) [1,2] and reduced ejection fraction (HFrEF) [3]. Improved clinical outcomes have also been reported in patients with HFrEF during chronic neuromodulation (NM) with carotid nerve plexus stimulation (CNPS) when baseline NT-proBNP < 1600 pg/ml [4]. Whether baseline NT-proBNP is associated with clinical responsiveness of patients with HFrEF to neuromodulation using vagus nerve stimulation (VNS) has not been examined. Therefore, we evaluated the interaction

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of baseline NT-proBNP with the changes in symptoms and function that occurred during chronic VNS in the ANTHEM-HF study.

2. Methods

ANTHEM-HF was an open-label, multicenter study that randomized 60 patients with HFrEF (LVEF $\leq$ 40%) and in NYHA 2 or 3 while on optimal medical management using guideline directed medical therapy (GDMT) to left or right cervical VNS for neuromodulation. The study protocol conformed to ethical guidelines of the 1975 Declaration of Helsinki, and informed consent was obtained from each patient. Optimal medical management before study entry required stable b-blocker therapy for HF as indicated and tolerated for 3 months, and stable doses as indicated and tolerated of all other oral pharmacologic therapy for HF, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, spironolactone, and loop diuretics for 1 month. NT-proBNP was collected for exploratory analysis and was not used for study entry. Changes in NYHA class, heart rate (HR), heart rate variability (HRV), left ventricular ejection fraction (LVEF), 6-min walk distance (6MWD) and Minnesota Living with HF score (MLWHF) were determined at baseline, three, and six months after VNS up-titration [5].

A repeated measures, generalized-estimating, equations model evaluated the relationship of symptomatic and functional responses to VNS to baseline NT-proBNP values above and below 1600 pg/ml. Summary descriptive statistics included t-tests and Wilcoxon tests for continuous variables, and chi-square tests for categorical measures [6].

3. Results

The median (interquartile range; maximum) NT-proBNP in ANTHEM-HF was 868 ([322, 1875]; 14,656) pg/ml. VNS was associated with significant improvements at 6 months in HR, HRV, LVEF, 6MWD, MLWHF, and NYHA in the study cohort, and there were no significant differences between the groups receiving right cervical VNS or left cervical VNS.5 The improvements in the overall study cohort were independent of baseline NT-proBNP [Table 1]. While there was a statistical interaction observed between baseline NT-proBNP and better LVEF during VNS, LVEF improved overall in the study cohort (N = 60; 32 ± 7 to 37 ± 10%; p = 0.0042), and in those patients whose baseline NT-proBNP was below the median baseline NT-proBNP value (n = 29; 36 ± 6 to 42 ± 10%; p < 0.0025)] or above this value (n = 29; 29 ± 7 to 32 ± 9%; p < 0.05) [Table 2]. NT-proBNP tended to decrease overall in association with VNS (Median [IQR]: 851 [313, 1951] to 714 [344, 1239]; p = NS).

4. Discussion

The findings from this analysis suggest that beneficial symptomatic and functional responses to VNS in patients with HFrEF may be independent of baseline NT-proBNP. The reasons for differences in the interaction between baseline NT-proBNP and the responses associated with chronic CNPS and VNS are unclear.

BeAT-HF is an ongoing open-label study that randomizes patients to CNPS plus continued GDMT versus continuation of GDMT alone as standard of care. NT-pro BNP elevation or previous HF hospitalization is used as an inclusion criterion. The study failed to demonstrate significant improvement in all three of its predetermined endpoints in the overall study cohort (N = 271), however, a post-hoc analysis successfully identified a sub-population of patients (n = 162) whose mean 6MWD, MLWHF, and NT-proBNP all improved if the baseline NT-proBNP was <1600 pg/ml.[4]

Some differences existed in the baseline clinical characteristics of the overall study cohort in the BeAT-HF when compared to ANTHEM-HF. The entry criteria for BEAT-HF required an EF $\leq$ 35% and NYHA class 3. Patients were allowed to enter the study after only one month of optimal pharmaceutical therapy using GDMT. Approximately 35% of patients in BEAT-HF had a history atrial fibrillation at the time of study entry, while a history of atrial fibrillation excluded patients from entry into ANTHEM-HF.

The median NT-proBNP at baseline (731, IQR 475, 1021) for the overall BEAT-HF study cohort (N = 264) was lower than in ANTHEM-HF (868, IQR 322, 1875). The net 16% decrease from baseline in median NT-proBNP during chronic VNS in ANTHEM-HF was modest, and its non-significance was unsurprising given the wide variability in NT-proBNP that can occur clinically and the small cohort of patients (N = 60) that was studied. By comparison, there was a net 10.5% decrease from baseline in median NT-proBNP in the overall study cohort in BEAT-HF during chronic CNPS, and a there was a net 9% decrease when patients receiving CNPS were compared to control patients. Neither of these decreases was significant.

There are several differences in the platform, stimulation site, and mode of stimulation for CNPS and VNS. Both utilize a generator implanted in the chest and an external programmer to adjust

Table 1
Repeated measures analysis of changes associated with VNS and relation to baseline NT-proBNP.

	Baseline[1]	6 months	Change[2]	p[3]	Regression Coefficient[4] for NT-proBNP	p[5]
HR	78 (10) [n = 60]	73 (11) [n = 57]	−4 (10)	0.0210	1.414 (−2.974, 5.802)	0.528
SDNN	92 (31) [n = 60]	111 (50) [n = 54]	17 (40)	0.0176	1.128 (−19.95, 22.206)	0.916
LVEF	32 (7) [n = 60]	37 (10) [n = 56]	5 (8)	0.0042	−6.547 (−10.60,−2.491)	0.002
6MWD	287 (66) [n = 60]	346 (78) [n = 57]	59 (85)	<0.0001	−25.64 (−58.24, 6.954)	0.123
MLWHFS	40 (14) [n = 60]	21 (10) [n = 57]	−18 (13)	<0.0001	0.881 (−3.569, 5.332)	0.698
NYHA[4]	0/33/24/0 [n = 57]	30/24/3/0 [n = 57]	77%[6]	<0.001	−0.387(−1.142, 0.367)	0.314

Legend:
[1] Mean (±standard deviation).
[2] Mean (±standard deviation) except NYHA.
[3] 6 months versus baseline.
[4] Coefficient (95% confidence interval).
[5] Significance of correlation.
[6] 77% of patients improved at 6 months.

Table 2
Relation of changes in symptoms and function to median baseline NT-proBNP.

	NT-proBNP < median (Group 1)				NT-proBNP > median (Group 2)				
	Baseline	6 mo	Change	p[1]	Baseline	6 mos	Change	p[1]	p[2]
HR	74 (8)	71 (11)	−3 (10)	NS	80 (11)	75 (10)	−5 (9)	<0.025	NS
SDNN	103 (25)	108 (37)	7 (2)	NS	85 (33)	115 (62)	28 (46)	<0.01	NS
LVEF	36 (6)	42 (10)	6 (9)	<0.0025	29 (7)	32 (9)	3 (7)	<0.05	NS
6MWD	295 (64)	345 (54)	49 (55)	<0.0001	276 (70)	346 (96)	69 (1 0 8)	<0.005	NS
MLWHFS	39 (12)	21 (9)	−17 (9)	<0.0001	41 (15)	21 (10)	−20 (16)	<0.0001	NS

Legend: Mean (±standard deviation).
[1] versus baseline.
[2] Group 1 versus Group 2.

stimulation. For CNPS, an electrical lead is placed on the carotid sinus nerve plexus that requires intra-operative mapping over the carotid arteries. The lead is fixed empirically over the anterior internal carotid artery adjacent to the carotid bifurcation when mapping does not identify an appropriate location [7]. For VNS, a self-sizing atraumatic lead is used and requires no intraoperative mapping for placement around the cervical vagus nerve.[5]

The intensity of CNPS is titrated postoperatively and uses electrical activation of carotid sinus baroreceptors to send signals through afferent neural pathways to the brainstem. These signals are interpreted within the vasomotor center as a rise in blood pressure, resulting in reflex effects that modulate autonomic signals to the heart, blood vessels, and kidneys, and causing vasodilation and inhibition of renin-angiotensin-aldosterone system and other activated neurohormones [8]. How CNPS is titrated, the relationship and magnitude of baroreceptor response to CNPS intensity, and the association of CNPS intensity and/or baroreceptor response with clinical response in BeAT-HF have yet to be entirely explained.

VNS intensity is also titrated postoperatively. Stimulation of the vagus nerve affects both central and peripheral neurotransmitters by facilitating or inhibiting the excitability of effector neurons to influence nervous system activity, and restores autonomic balance by increasing parasympathetic activity and reducing sympathetic tone [9]. Changes in HR and HRV serve as biomarkers to determine when a satisfactory level of autonomic nervous system engagement (ANSE) has been reached. Achieving ANSE appears to be "dose dependent", based upon the stimulation frequency, amplitude, pulse width and duty cycle used for VNS delivery [10].

ANTHEM-HF was an uncontrolled study, and it is possible that the overall effect sizes may not have been solely attributable to VNS alone. It is also possible that the improvements in the more subjective assessments in both studies may have been related to a Hawthorne effect.

Whether there may be differing effects of CNPS and VNS on cardiovascular remodeling and function also remains to be determined. No data is available from BEAT-HF concerning changes in LV structure or function in response to CNPS. Significant improvements occurred in ANTHEM-HF in the objective measures of HR, HRV, and LVEF in association with VNS, and these provide a potential "biological plausibility" for the improvements that were observed in the more subjective measures of 6MWD, NYHA class, and quality of life [11] Beneficial effects in patients receiving chronic VNS have persisted for up to 42 months VNS [5,12,13].

Hence, the findings from this analysis should be considered preliminary and hypothesis-generating. An ongoing trial, BIRD-HF, is evaluating whether changes in LVESVi and LVEF may occur with CNPS [14]. Additional insights may come from the ongoing ANTHEM-HFrEF Pivotal Study, a multinational, multicenter, randomized, controlled trial that is comparing the use of VNS in addition to GDMT to improve outcomes for patients with HFrEF [15,16].

5. Conclusions

Clinical and functional responses in patients with HFrEF to neuromodulation using VNS may be independent of baseline NT-proBNP. These are preliminary and hypothesis-generating findings. The reason for a differing interaction between baseline NT-proBNP and response to CNPS and VNS remains unclear. The ongoing BIRD-HF study is assessing whether changes occur in cardiovascular structure and function in response to CNPS, and will hopefully also address how CNPS is titrated, the relationship and magnitude of baroreceptor response to CNPS intensity, and their association with clinical response. Additional insights will come from the ongoing ANTHEM-HFrEF Pivotal Study of VNS.

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CRediT authorship contribution statement

Inder Anand: Conceptualization, Writing - original draft. **Jeffrey L. Ardell:** Writing - review & editing. **Doug Gregory:** Methodology, Formal analysis, Validation, Writing - review & editing. **Imad Libbus:** Data curation, Writing - review & editing. **Lorenzo DiCarlo:** Conceptualization, Writing - review & editing. **Rajendra K. Premchand:** Investigation. **Kamal Sharma:** Investigation. **Sanjay Mittal:** Investigation. **Rufino Monteiro:** Investigation.

Declaration of Competing Interest

RP, KS, SM, and RM were compensated by Cyberonics Incorporated for their work as clinical investigators in the ANTHEM-HF Pilot Study. IA is a clinician, JLA is a researcher in neurocardiology, and DDG is a statistician who are contracted as consultants to LivaNova USA Incorporated. IL and LDC are employees and shareholders of LivaNova USA Incorporated.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100520.

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