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Lack of improvement in autonomic cardiac tone after sacubitril/valsartan at lower than target doses

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ABSTRACT

Autonomic regulation plays a role in the progression of heart failure with reduced ejection fraction (HrEF). Twenty-one HFrEF patients, 60.8 ± 13.1 years, receiving angiotensin inhibition, were replaced by angiotensin receptor-neprilysin inhibitor (ARNI). A 24-hour Holter recording was performed before and after 3 months of the maximum tolerated dose of ARNi. We evaluated changes in autonomic tone using heart rate variability (SDNN, rMSSD, pNN50, LF, HF, LF/HF, α1, α2), and heart rate turbulence (TO and TS). ARNI was up-titrated to a maximum daily dose of 190 ± 102 mg, 47.5% of the target dose. ARNI therapy was not associated with any improvement in any of the parameters related with heart rate variability or heart rate turbulence ($p > 0.05$ for all). ARNI use at lower than target doses did not improve autonomic cardiac tone as evaluated by 24-hour Holter monitoring.

Evidence-based therapies for heart failure with reduced ejection fraction (HrEF) patients have demonstrated a favorable effect by improving autonomic imbalance, which is thought to contribute in part to its beneficial effects [1–4]. The aim of the study was to evaluate the effect of angiotensin receptor-neprilysin inhibitor (ARNI), on the autonomic tone of patients with HrEF in clinical practice by using Holter-derived parameters.

From October 2016 to June 2017, 21 patients with an established diagnosis of stable HFrEF met the eligibility criteria: 1) left ventricular ejection fraction <40%; 2) non-paced normal sinus rhythm and 3) patients who, following the clinical criteria of the responsible cardiologist, were changed from an angiotensin enzyme-converter inhibitor (ACEi) or angiotensin receptor blocker (ARB) to an ARNI. This compound was approved by US Food and Drug Administration to reduce the risk for cardiovascular death and hospitalization in HrEF patients. Before this switch, an ambulatory 24-hour Holter was carried out (ELA Medical, Sorin Group, Paris, France). ARNI was started and up-titrated following the criteria of the responsible cardiologist and normal clinical practice. After 3 months of receiving the maximum tolerated dose of ARNI, a new ambulatory 24-hour Holter was performed. The protocol was approved by the research ethics committee, in accordance with the principles of the Helsinki Declaration, and all patients provided written informed consent.

To evaluate heart rate variability (HRV), the standard deviation of all normal RR intervals (SDNN), root-mean square differences of successive R-R intervals (rMSSD) and the percentage of adjacent normal RR intervals differing by >50 ms (pNN50) were chosen as representative non-spectral indexes of short-period heart rate. HRV was analyzed using spectral methods: low frequency (LF) (0.04–0.15 Hz) band, high frequency (0.15–0.40 Hz) band and LF/HF ratio. We also evaluated the detrended fluctuation of HRV, calculating a short-term fractal exponent, α1, and a long-term fractal exponent, α2. With respect to HRT parameters, two parameters were calculated: turbulence slope (TS) and turbulence onset (TO).

Continuous variables were tested for a normal distribution with the Kolmogorov-Smirnov test. Normally distributed data are presented as mean ± SD and non-normally distributed data as median with interquartile range. Categoric variables are expressed as percentages. A paired Student *t*-test or Wilcoxon paired test was used to compare continuous variables. Data were processed using SPSS version 21 (SPSS, Inc.,

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Table 1
Baseline clinical and biochemical characteristics (n = 21).

Age, years	60.8 ± 13.1
Male	11 (52)
Diabetes Mellitus	5 (23)
Hypertension	7 (30)
Non-ischemic aetiology	14 (67)
New York Heart Association class	2.5 ± 0.5
Left ventricular ejection fraction, %	27 ± 4
Creatinine, mg/dL	0.9 ± 0.2
Haemoglobin, g/dL	12.0 [11.0–13.2]
Sodium, mg/dL	140 [138–141]
NT-proBNP, pg/mL	912 [643–1225]
Current treatment at inclusion	
Beta-blockers	19 (90)
% target dose	51 ± 33
ACEi/ARB	21 (100)
% target dose	71 ± 33
Aldosterone Antagonist	19 (90)
% target dose	65 ± 24
Loop diuretics	21 (100)
Amiodarone	10 (20)
Implantable cardioverter-defibrillator	12 (57)

Data are expressed as mean (standard deviation), median (interquartile range) or percentages. NT-proBNP: N-terminal prohormone of brain natriuretic peptide; ACEi: angiotensin enzyme-converter inhibitor; ARB: angiotensin receptor blocker.

Chicago, Illinois). A p value ≤ 0.05 was considered statistically significant.

Twenty-one ambulatory patients with HFrEF met the eligibility criteria and were enrolled in the study. The baseline characteristics are listed in Table 1.

Treatment with ACEi or ARB was replaced by ARNI at the maximum tolerated dose of 190 ± 102 mg, which represented 47.5% of the target dose. No differences were found in NT-proBNP levels after 3 months of ARNI: median 912 [IQR: 643–1225] pg/ml vs. 845 [IQR: 610–1200] pg/ml (p = 0.32).

Before the initiation of ARNI, there was a high correlation between SDNN and LF (r = 0.907, p < 0.001), rMSDD with both pNN50 (r = 0.788, p = 003) and LF (r = 0.930, p < 0.001) and LF/HF with α1 (r = 0.765, p = 0.006). The temporal evolution of the HRV and HRT parameters is summarized in Table 2. As shown, no statistically significant differences were found in any of these parameters after 3 months of therapy.

Table 2
Holter parameters before and after ARNI treatment.

	Before ARNI	3 months after ARNI	p-Value
Time-domain measures			
SDNN, ms	42.1 ± 11.5	38.3 ± 12.3	0.100
rMSSD, ms	22.2 ± 8.2	23.3 ± 11.6	0.671
pNN50, %	3.4 [2.0–5.7]	2.8 [1.4–6.3]	0.709
Frequency measures			
LF, ms^2	297 [187–450]	189 [119–388]	0.093
HF, ms^2	117 [74–185]	109 [58–198]	0.370
LF/HF	2.6 [1.7–4.1]	2.3 [1.7–3.3]	0.147
Detrended fluctuation analysis			
α1	1.20 ± 0.2	1.16 ± 0.2	0.470
α2	1.09 ± 0.1	1.10 ± 0.1	0.375
Heart rate turbulence			
TO, %	−0.67 [−1.08–0.01]	−0.16 [−1.30–0.57]	0.134
TS, ms/RR	3.36 [2.01–5.75]	2.89 [1.54–4.90]	0.679
PVC per 24 h	449 [199–1502]	586 [51–2854]	0.821

SDNN: standard deviation of all normal RR intervals; rMSSD: root-mean square differences of successive R-R intervals; pNN50: percentage of adjacent normal RR intervals >50 ms different; LF: low frequency (0.04–0.15 Hz) band; HF: high frequency (0.15–0.40 Hz) band; TO: turbulence onset; TS: turbulence slope. PVC, premature ventricular contractions.

The major finding of the present study is that ARNI used at lower than target doses did not improve autonomic tone, as evaluated with several indexes obtained by using 24-hour Holter monitoring.

Neurohormonal antagonists have been shown to improve survival in patients with HrEF. These include the use of ACEi or ARB, betablockers and aldosterone antagonists [1–3]. Moreover, cardiac resynchronization is also able to modify the autonomic balance, as defined by HRV measurements [4]. Thus, improvement in HRV may be one of the mechanisms explaining the benefits of evidence-based therapies for preventing HFrEF progression and sudden cardiac death. Recently, a new compound, ARNI [5] has been shown to be better than enalapril for reducing the risk of cardiovascular and sudden cardiac death and also heart failure hospitalizations. The aim of our study was to explore meaningful pathophysiological mechanisms that would explain these clinical benefits. We found no improvement in any of the autonomic parameters studied, including the density of ventricular ectopy. However, De Diego et al. [6] in a recent study pointed to a reduction of ventricular arrythmias as a potential underlying mechanism to explain part of the benefits of this drug. Although the final dose of ARNI was not reported in that study, there was a significant decrease in NT-proBNP levels, contrary to our findings. This may reflect an insufficient ARNI dose in our patients, unable to also improve autonomic tone.

The evaluation of autonomic tone after a short period of 3 months with the maximum tolerated dose of ARNI should be regarded with caution. However other evidence-based therapies have demonstrated an early improvement in autonomic imbalance [1–3]. Another limitation is that patients tolerated and therefore received lower than target doses.

In conclusion, no improvement in electrical remodeling was found in our population after initiation of ARNI, as compared with previous treatment with ACEi (or ARB). Whether higher doses or a longer period on therapy would translate into different findings needs further study.

Disclosures

None.

References

[1] Malfatto G, Facchini M, Branzi G, Riva B, Sala L, Perego GB. Long-term treatment with the beta-blocker carvedilol restores autonomic tone and responsiveness in patients with moderate heart failure. J Cardiovasc Pharmacol 2003;42(1):125–31.
[2] Zhang YH, Song YC, Zhu J, Hu TH, Wan LL. Effects of enalapril on heart rate variability in patients with congestive heart failure. Am J Cardiol 1995;76(14):1045–8.
[3] Yee KM, Pringle SD, Struthers AD. Circadian variation in the effects of aldosterone blockade on heart rate variability and QT dispersion in congestive heart failure. J Am Coll Cardiol 2001;37(7):1800–7.
[4] Fantoni C, Raffa S, Regoli F, Giraldi F, La Rovere MT, Prentice J, et al. Cardiac resynchronization therapy improves heart rate profile and heart rate variability of patients with moderate to severe heart failure. J Am Coll Cardiol 2005;46(10):1875–82.
[5] McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371(11):993–1004.
[6] de Diego C, González-Torres L, Núñez JM, Centurión Inda R, Martin-Langerwerf DA, Sangio AD, et al. Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices. Heart Rhythm 2017. https://doi.org/10.1016/j.hrthm.2017.11.012 pii: S1547-5271(17)31331-0. (Epub ahead of print).