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ORIGINAL RESEARCH

Angiotensin Receptor-Neprilysin Inhibitor Is Associated With Improved Cardiac Autonomic Function in Heart Failure

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BACKGROUND: Heart failure with reduced ejection fraction is associated with potentially deleterious imbalance of the cardiac autonomic nervous system. Sacubitril/valsartan (angiotensin receptor-neprilysin inhibitor [ARNI]) reduces cardiovascular mortality and hospitalization for heart failure with reduced ejection fraction. Whether ARNI affects the cardiac autonomic nervous system has not been studied.

METHODS AND RESULTS: This investigator-initiated, prospective, single-center cohort study compared heart rate (HR) variability, HR, deceleration capacity, and periodic repolarization dynamics as noninvasive measures of the cardiac autonomic nervous system before and after initiation of ARNI therapy. Patients underwent standardized 12-lead Holter-ECG, echocardiography and laboratory testing before and 3 months after start of therapy. End points were changes in HR variability (SD of normal-to-normal intervals, mean square of differences between consecutive R-R intervals), HR, deceleration capacity, and periodic repolarization dynamics as well as ventricular function and NT-proBNP (N-terminal pro-B-type natriuretic peptide). Of 63 patients with heart failure with reduced ejection fraction enrolled, 48 (76.2%) patients were still on ARNI at follow-up. SD of normal-to-normal intervals increased from 25 to 36 milliseconds (P<0.001), mean square of differences between consecutive R-R intervals increased from 12 to 19 milliseconds (P<0.001), HR decreased from 73±9 bpm to 67±4 bpm, (P<0.001), and deceleration capacity increased from 2.1 to 4.4 milliseconds (P<0.001). A trend for periodic repolarization dynamics reduction was observed (5.6 deg^2 versus 4.7 deg^2, P=0.09). Autonomic changes were accompanied by increased left ventricular ejection fraction (29±6% versus 40±8%, P<0.001) and reduced NT-proBNP (3548 versus 685 ng/L, P<0.001). Correlation analysis showed a significant relationship between volume-unloading (as evidenced by NT-proBNP reduction) and autonomic improvement.

CONCLUSIONS: Three months of ARNI therapy resulted in a significant increase in cardiac parasympathetic tone. The improvement in autonomic properties may be mediated by "volume unloading" and likely contributes to the beneficial effects of ARNI in heart failure with reduced ejection fraction.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique Identifier: NCT04587947.

Key Words: ARNI ■ cardiac autonomic nervous system ■ heart failure ■ heart rate variability ■ parasympathetic

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CLINICAL PERSPECTIVE

What Is New?

- Angiotensin receptor-neprilysin inhibitor therapy leads to a favorable modulation of cardiac autonomic nervous system by increasing parasympathetic activity.
- Autonomic rebalancing is presumably mediated by "volume unloading" in response to angiotensin receptor-neprilysin inhibitor therapy.

What Are the Clinical Implications?

- The combination of improvement in structural cardiac function and autonomic cardiac properties may explain the reduction in ventricular arrhythmias observed with angiotensin receptor-neprilysin inhibitor and contribute to reduced morbidity and mortality among treated patients with heart failure with reduced ejection fraction.
- The positive effect on autonomic properties provides additional support for the earliest possible use of angiotensin receptor-neprilysin inhibitor therapy in patients with heart failure with reduced ejection fraction.

Nonstandard Abbreviations and Acronyms

CANS	cardiac autonomic nervous system
DC	deceleration capacity
HRV	heart rate variability
PRD	periodic repolarization dynamics
RMSSD	mean square of differences between consecutive R-R intervals
SDNN	SD of normal-to-normal intervals

Heart failure (HF) importantly contributes to mortality in Western populations with its overall age-related prevalence of ~1% to 2% and a 5-year survival rate of only ~40% to 50%.[1–3] Mortality in HF with reduced ejection fraction (HFrEF) has been linked with dysfunction and imbalance of cardiac autonomic nervous system (CANS).[4,5] Autonomic balance between the parasympathetic and sympathetic cardiac nervous system typically shifts toward sympathetic overactivity due to dysfunction of sympatho-inhibitory reflexes associated with increased end-diastolic pressure and decreased stroke volume.[6–9]

An SD of normal-to-normal intervals (SDNN) <50 milliseconds identifies patients at high risk of death (51.4% per year).[4] In addition, in patients post myocardial infarction, CANS dysfunction is an established predictor of all-cause mortality.[10–12] Deceleration capacity (DC, parasympathetic activity) and periodic repolarization dynamics (PRD, sympathetic activity) were identified as superior predictors for mortality after myocardial infarction compared with left ventricular ejection fraction (LVEF) or conventional heart rate variability (HRV) parameters.[10–12] Recently, 2 independent trials demonstrated that increased PRD predicts reduction in mortality associated with prophylactic implantation of cardioverter-defibrillators in patients with ischemic and nonischemic cardiomyopathy.[13,14]

Sacubitril/valsartan (ARNI) reduces the risk of cardiovascular mortality and HFrEF hospitalization[15] and may even reduce the incidence of ventricular arrhythmia and implantable cardioverter-defibrillator shocks in patients with HFrEF, suggesting "antiarrhythmic" properties.[16]

Sparse mechanistic data are available on how ARNI exerts its beneficial effects, and the influence of ARNI therapy on CANS is largely unknown. Accordingly, we hypothesized that initiation of ARNI would improve autonomic function in patients with HFrEF.

METHODS

Study Design

The present trial was an investigator-initiated, prospective observational, single-center cohort study with predefined primary end points conducted at St Josefs-Hospital (Wiesbaden, Germany) between October 2020 and June 2022. We enrolled consecutive patients affected by HFrEF who were scheduled for initial ARNI therapy. Therapy was initiated in accordance with the current 2021 European Society of Cardiology guideline for the diagnosis and management of acute and chronic HF independently of this study.[17] All patients provided written informed consent for study participation. The study was approved by the regional ethics committee (Landesaerztekammer Hessen, III/1/ker F 9/2019), registered at clinicaltrials.gov (NCT04587947), and followed the rules of the Declaration of Helsinki. The data that support the findings of this study are available in an anonymized form from the corresponding author upon request.

Hypothesis and End Points

In light of a previous case report,[18] we hypothesized that ARNI therapy positively influences CANS function as measured by a significant improvement in SDNN. Against this background, improvement in SDNN was chosen as the primary end point. Mean square of differences between consecutive R-R intervals (RMSSD), HR, DC, and PRD, as well as echocardiographic and neurohumoral (NT-proBNP [N-terminal pro B-type natriuretic peptide], ng/L) changes were analyzed secondarily.

Statistical Analysis

This study was designed to demonstrate an ARNI-induced improvement in cardiac autonomic function. Based on preliminary HRV evaluation in patients with HFrEF at our center, we estimated mean SDNN in this cohort to be 30±12 milliseconds and defined a 10 milliseconds increase (+33%) as a significant improvement. For this purpose, a fixed sample size design was chosen. For a power of 80% with an alpha of 5% (2-sided) inclusion of 45 patients was required. With an anticipated dropout rate of 20%, expected loss-to-follow-up rate of 10%, and a safety margin of 10%, this resulted in a sample size of 63 patients.

Because the choice of analysis form based on preliminary normality tests can seriously affect the calibration of small samples,[19] all variables were instead analyzed by a permutation test with 10 000 repetitions comparing mean values at baseline and follow-up. Pearson correlation method was used to analyze the (in)dependency of possible effects. Significance level was set at 0.05.

Given their general lack of normal distribution, HRV and NT-proBNP values are presented as median and interquartile ranges (IQR). All other parameters are presented as mean±SD. Statistical analyses were performed using R version 4.3.2 (R Core Team 2021), PRISM software version 9 (GraphPad™, San Diego, CA) and SPSS version 28 (IBM™, Armonk, NY).

Inclusion and Exclusion Criteria

Patients >18 years of age with HFrEF (defined as LVEF ≤40%[17]) and an indication for ARNI therapy were included in the study after providing written informed consent. Exclusion criteria were contraindication for ARNI therapy, atrial fibrillation, presence of cardiac implantable electronic device, lack of consent capacity, or concomitant study participation.

Baseline Examination and Follow-Up

Immediately before initiation of ARNI therapy (<7 days), transthoracic echocardiography and blood sampling were performed in addition to measurement of HRV (SDNN and RMSSD), HR, DC, and PRD.

ECG recordings were obtained with a 12-lead Holter-ECG device (SpiderView; MicroPort CRM, Paris, France), corresponding memory cards, and BlueSensor VL ECG electrodes (Ambu, Bad Nauheim, Germany). To obtain measurements at rest and under autonomic stimulation, ECG measurements were recorded in supine position (30 minutes) followed by standing position (10 minutes).

The following echocardiographic parameters were evaluated: LVEF, LV stroke volume index, LV end-diastolic volume index (LVEDV index), left ventricular end-systolic volume index (LVESV index), left atrial end-systolic volume index, degree of mitral regurgitation, tricuspid annular plane systolic excursion, pulmonary artery pressure, and right ventricular/pulmonary arterial coupling (calculated by tricuspid annular plane systolic excursion/pulmonary artery pressure).

Follow-up was performed at 3 months. In order to account for environmental differences, baseline and follow-up recordings were obtained in an identical setting at the same time of the day with at least 2 hours after meal intake. In order to additionally avoid unintended influences on CANS (eg, due to exertion on the way to the examination room), autonomic measurement was first initiated after 10 minutes of rest in a lying position and all patients were instructed to take their medication regularly.

Technical Aspects of HRV, DC, and PRD Analysis

CANS function can be assessed noninvasively by analysis of biosignals recorded from the body surface.[20] SDNN represents an estimate of overall HRV (with parasympathetically-mediated respiratory sinus arrhythmia being the primary source in short-term resting recordings). RMSSD reflects beat-to-beat variance in HR and represents the primary HRV measure used to estimate parasympathetic-mediated changes in HRV.[20,21]

DC and PRD represent advanced digital biomarkers related to parasympathetic and sympathetic dysregulation that can be applied for mortality risk stratification following myocardial infarction.[10–12] DC detects predominantly parasympathetic tonic influences at the level of the sinus node and is calculated by detecting anchor points (RR intervals that are longer than the previous one), aligning segments of same size at the anchors (phase rectification), signal averaging, and quantifying DC.[10] Reference values for DC divide patients into 3 risk levels with respect to mortality after myocardial infarction: high risk (≤2.5 milliseconds), intermediate risk (2.6 to 4.5 milliseconds), and low risk (>4.5 milliseconds).[10]

PRD is an electrocardiographic phenomenon whose determination is based on vector electrography methods and reflects low-frequency undulations of ventricular repolarization instability. Experimental studies suggest that low-frequency undulations are caused by efferent phasic sympathetic nerve activity.[22] Thus, PRD demonstrates an expression of efferent sympathetic activity at the level of the ventricular myocardium.[11] PRD is not subject to HRV or respiratory sinus arrhythmia and values ≥5.75 deg^2 identify patients at high risk of death after myocardial infarction.[11]

An individual evaluation of HR, HRV, DC, and PRD was carried out with the help of SMARTlab (Medical University Hospital Innsbruck, Austria).

RESULTS

Patient Population

We enrolled 63 consecutive patients, of whom 9 patients had to discontinue ARNI therapy due to symptomatic hypotension or other intolerance and 6 patients withdrew consent. Apart from a lower proportion of men (60% versus 88%, P=0.03), there were no differences in baseline characteristics between these 15 patients compared with the 48 (76%) patients who were still on ARNI therapy at follow-up (Table S1).

Therefore, the analysis was based on data obtained from the 48 subjects who completed follow-up. Mean age was 66±12 years, 88% were male, and 63% had underlying ischemic cardiomyopathy. Baseline characteristics are displayed in Table 1.

Compared with the initial dose after inclusion, ARNI dose was significantly increased at follow-up (106±24 mg versus 183±88 mg, P<0.001). There was no difference in the dosage of concomitant HF medications between baseline and follow-up: beta blocker (rate of maximum beta-blocker dose: 0.38±0.3 versus 0.41±0.26, P=0.22), sodium-glucose cotransporter-2 inhibitor (5±6 mg versus 6±6 mg, P=0.44), loop diuretics (5±5 mg versus 5±5 mg, P=0.82), or mineral receptor antagonist (29±13 mg versus 26±15 mg, P=0.46).

Heart Rate Variability, Heart Rate, and Blood Pressure

The primary end point was achieved as evidenced by a significant increase in SDNN with ARNI therapy at rest [25 milliseconds (IQR 18–37 milliseconds) versus 37 milliseconds (IQR 25–55 milliseconds), P<0.001] and in standing position [25 milliseconds (IQR 18–32 milliseconds) versus 36 milliseconds (IQR 27–50 milliseconds), P<0.001; Figure 1A]. Primary end point achievement was accompanied by a significant increase in RMSDD [supine: 12 milliseconds (IQR 7–19 milliseconds) versus 19 milliseconds (IQR 12–29 milliseconds), P<0.001; standing position: 10 milliseconds (IQR 7–14 milliseconds) versus 15 milliseconds (IQR 10–20 milliseconds), P<0.001; Figure 1B] and decrease in HR (supine: 73±9 bpm versus 67±4 bpm, P<0.001; standing position: 80±9 bpm versus 75±11 bpm, P<0.001; Figure 2C).

Systolic (RR_{sys}) and diastolic (RR_{dia}) blood pressure significantly decreased after 3 months of ARNI therapy (RR_{sys}: 135±19 mm Hg versus 113±14 mm Hg, P<0.001 and RR_{dia}: 81±14 mm Hg versus 68±14 mm Hg, P<0.001).

Table 1. Baseline Characteristics of Patients Included in the Study

Parameter	
Age, y	66±12
Male sex	42 (88%)
Ischemic cardiomyopathy	30 (63%)
Nonischemic dilatative cardiomyopathy	18 (37%)
Arterial hypertension	29 (60%)
Coronary artery disease	34 (71%)
Diabetes	14 (29%)
Hyperlipidemia	15 (31%)
Chronic obstructive pulmonary disease	7 (15%)
Obstructive sleep apnea syndrome	1 (2%)
Peripheral arterial disease	7 (13%)
Previous stroke	7 (15%)
Impaired renal function (glomerular filtration rate<60 mL/min)	16 (33.3%)
Active smoker	24 (50%)

Deceleration Capacity and Periodic Repolarization Dynamics

DC was significantly increased at rest (2.1 milliseconds [IQR −0.6 to 4.4 milliseconds] versus 4.4 milliseconds [IQR 2.4–6.9 milliseconds], P<0.001) and in standing position (2.2 milliseconds [IQR 0.5–3.3 milliseconds] versus 2.6 milliseconds [IQR 1.4–5 milliseconds], P=0.02; Figure 2A). A trend for a decrease in PRD under resting conditions was observed (supine: 5.6 deg^2 [IQR 3.5–10.7 deg^2] versus 4.7 deg^2 [IQR 2.6–8.5 deg^2], P=0.09; Figure 2B) whereas no difference was found in standing position (8.4 deg^2 [IQR 5.5–13.7 deg^2] versus 8.8 deg^2 [IQR 5.9–11.8 deg^2], P=0.69).

A sensitivity analysis comparing PRD values between patients with ischemic cardiomyopathy and nonischemic dilated cardiomyopathy can be found in Figures S1 and S2.

Echocardiographic Findings and Blood Samples

Echocardiography demonstrated a significant increase in LVEF (29±6% versus 40±8%, P<0.001), LV stroke volume index (24±7 mL/m^2 versus 27±7 mL/m^2, P<0.001), and tricuspid annular plane systolic excursion, representing an estimation of right ventricular function (19±5 mm versus 21±4 mm, P<0.001) along with a significant reduction in LVEDV index (86±28 mL/m^2 versus 71±24 mL/m^2, P<0.001), LVESV index (62±25 mL/m^2 versus 44±22 mL/m^2, P<0.001), left atrial end-systolic volume index (38±10 mL/m^2 versus 31±10 mL/m^2, P<0.001), visual degree of mitral regurgitation (1.3±0.9 versus 0.7±0.7, P<0.001; vena contracta: 3 mm±2.5 mm versus 1.4±1.7 mm, P<0.001), and pulmonary artery pressure (42±11 mm Hg versus 26±13 mm Hg, P=0.01). Right ventricular/pulmonary arterial -coupling (tricuspid annular plane systolic excursion/pulmonary artery pressure), an index of the relationship between right ventricular contractility and right ventricular afterload, was increased

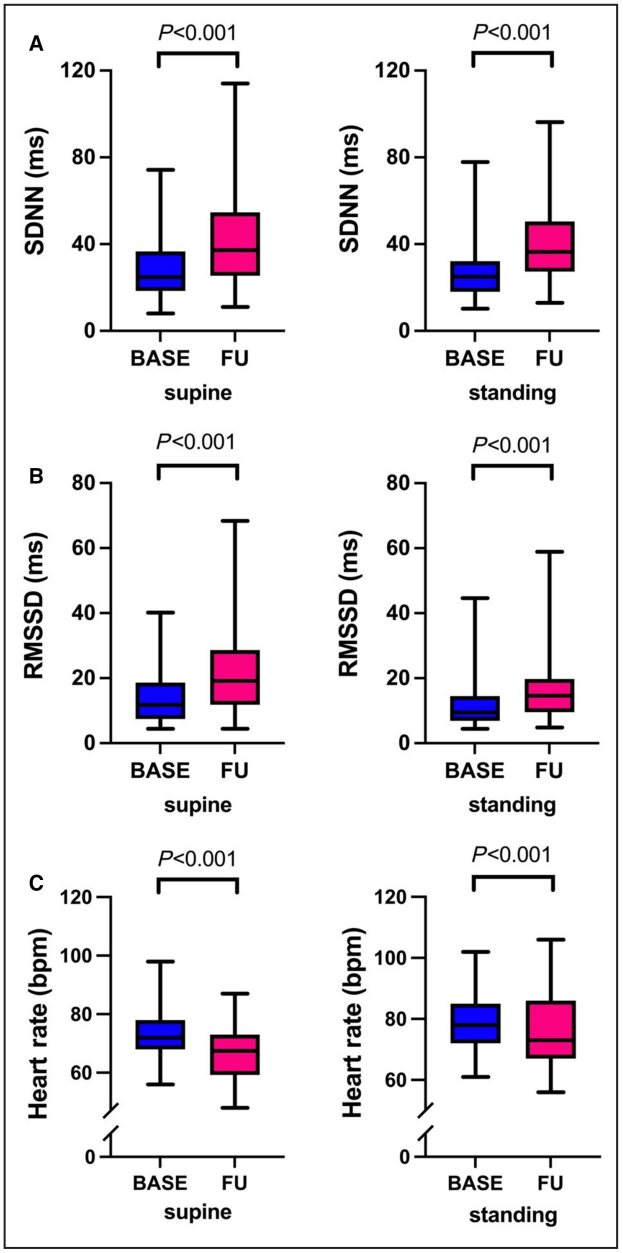

Figure 1. Comparison of heart rate variability (SDNN [A], RMSSD [B], and HR [C]) in supine and standing position at baseline and after 3 months of ARNI therapy.
ARNI indicates angiotensin receptor-neprilysin inhibitor sacubitril/valsartan; BASE, baseline; FU, follow-up; HR, heart rate; RMSSD, mean square of differences between consecutive R-R intervals; and SDNN, SD of normal-to-normal intervals.

(0.47±0.19 mm/mm Hg versus 1.08±0.72 mm/mm Hg, *P*=0.004), indicating a significant improvement in right ventricular hemodynamics (Table 2).

These findings were accompanied by reduced plasma NT-proBNP levels (3548 ng/L [IQR 1953–6710 ng/L] versus 685 ng/L [IQR 281–1135 ng/L]; *P*<0.001) and increased hemoglobin (12.5±2.1 g/dL versus 13.9±1.7, *P*<0.001) and hematocrit levels (38±7% versus 42±5%, *P*<0.001). Serum creatinine values remained unaffected (1.2±0.4 mg/dL versus 1.2±0.3 mg/dL, *P*=0.60). Figure 3 illustrates the structural and autonomic effects of 3-month ARNI therapy demonstrated in this study.

To investigate whether changes in CANS after ARNI therapy were related to improvement in structural-cardiac properties (expressed by improvement in LVEF) or cardiac volume status (expressed by NT-proBNP), correlation analysis was performed based on changes before and after ARNI therapy at rest. Whereas no association was found between the improvement in CANS function and LVEF, a significant relationship between improvement in NT-proBNP and changes in SDNN, RMSSD, and HR were demonstrated (Table 3).

DISCUSSION

Main Findings

The present study demonstrated increases in HRV and DC as well as decreases in HR after initiation of ARNI, suggesting augmentation of parasympathetic tone.

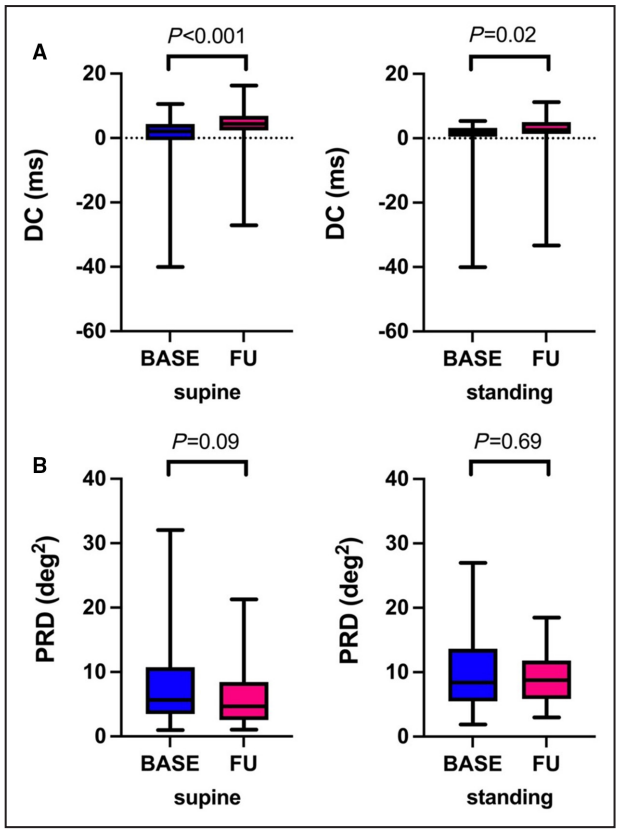

Figure 2. Effect of ARNI therapy on autonomic markers.
Comparison of DC (**A**) and PRD (**B**) in supine and standing position at baseline and after 3 months of ARNI therapy. ARNI indicates angiotensin receptor-neprilysin inhibitor sacubitril/valsartan; BASE, baseline; DC, deceleration capacity; FU, follow-up; and PRD, periodic repolarization dynamics.

Table 2. Echocardiographic Findings Before and 3 Months After Initiation of ARNI Therapy

Parameter	Baseline	Follow-up	*P* value
Left ventricular ejection fraction, %	29±6%	40±8%	<0.001
Left ventricular stroke volume index, mL/m^2	24±7	27±27	0.001
Left ventricular end-diastolic volume index, mL/m^2	85±27	70±25	<0.001
Left ventricular end-systolic volume index, mL/m^2	60±22	44±22	<0.001
Mitral regurgitation (grade)	1.3±0.9	0.7±0.7	<0.001
Tricuspid annular plane systolic excursion, mm	19±5	21±4	<0.001
Pulmonary artery systolic pressure, mm Hg	42±11	26±13	0.01
Right ventricular/pulmonary arterial coupling, mm/mm Hg	0.47±0.19	1.08±0.72	0.004
Left atrial end-systolic volume index, mL/m^2	38±10	31±10	<0.001

These results were accompanied by an improvement in left and right ventricular function and reduction in plasma NT-proBNP levels representing a potentially beneficial modulation of CANS by ARNI therapy.

Autonomic Tone and Ventricular Arrhythmias

CANS plays an integral role in the development of ventricular arrhythmias, particularly in patients with myocardial infarction or HFrEF.[23] Sympathetic excitation can precipitate ventricular tachyarrhythmias and parasympathetic activation can be protective.[24] HRV as a measure of autonomic tone has been extensively investigated and impaired HRV is a marker of increased mortality in patients with HFrEF[4,5] and a significant predictor of mortality and cardiovascular events even in the absence of cardiovascular disease.[25,26]

The PARADIGM-HF (Angiotensin-Neprilysin Inhibition Versus Enalapril in Heart Failure)-Trial demonstrated superiority of ARNI therapy in patients with HFrEF regarding risk of cardiovascular mortality and HFrEF hospitalizations compared with enalapril.[15] These benefits have been attributed primarily to the properties of ARNI to promote cardiac reverse remodeling, improve systolic LV function, and possibly reduce fibrosis burden.[27–29]

In PARADIGM-HF the majority of deaths were sudden cardiac and these were significantly reduced by treatment with ARNI.[30] De Diego et al reported a significantly lower incidence of ventricular arrhythmia and implantable cardioverter-defibrillator shocks in patients with HFrEF after switching from angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to ARNI therapy.[16]

Potential Underlying Mechanism

In patients with HFrEF, the increase in sympathetic outflow with a simultaneous decrease in parasympathetic HR modulation is primarily attributed to a dysfunction of sympatho-inhibitory reflexes[8]: Although the arterial baroreflex control of sympathetic nerve activity appears to be intact in human HF,[6] cardiopulmonary baroreceptor reflexes may be impaired in the context of previous myocardial infarction, potentially less stimulated with decreasing inotropy, or altered by ventricular dilatation and thus further impair reflex sympathetic inhibition.[8,9]

According to our results, ARNI therapy may lead to a restoration of sympatho-inhibitory reflexes, increased parasympathetic influence, and thus autonomic rebalancing. This ARNI effect on CANS balance is potentially mediated by "volume unloading" as suggested by the following results:

1. Significant decrease in NT-proBNP. The (NT-pro) BNP concentration is known to positively correlate with a patient's volume status,[31,32] with LVEDV/LVESV indices and myocardial wall stress.[33] A reduction in BNP can therefore be interpreted as an expression of "volume unloading." This assumption is supported by the observed increase in hematocrit.
2. Significant increase in HRV and DC. Atrial stretching results in decreased total HRV (SDNN) and parasympathetic components of HRV.[34] Similarly, ventricular wall stress is associated with depressed HRV.[35] Volume overload is associated with impaired HRV in patients with chronic kidney disease on hemodialysis and normalization of volume status results in improved HRV.[36] In our study improvement in HRV (SDNN, RMSSD) was significantly related to volume unloading, as evidenced by NT-proBNP reduction.
3. Significant decrease in LVEDV index and LVESV index and an increase in LVEF and LV stroke volume index. Decreased LV dilatation and increased inotropy may "reset" cardiopulmonary baroreceptors and restore sympatho-inhibitory reflexes.
4. Decrease in blood pressure and HR. Because a reduction in blood pressure (causing a decrease in vascular wall stretch detected by arterial baroreceptors) usually leads to an increase in HR,[37] our results with evidence of a decrease in HR

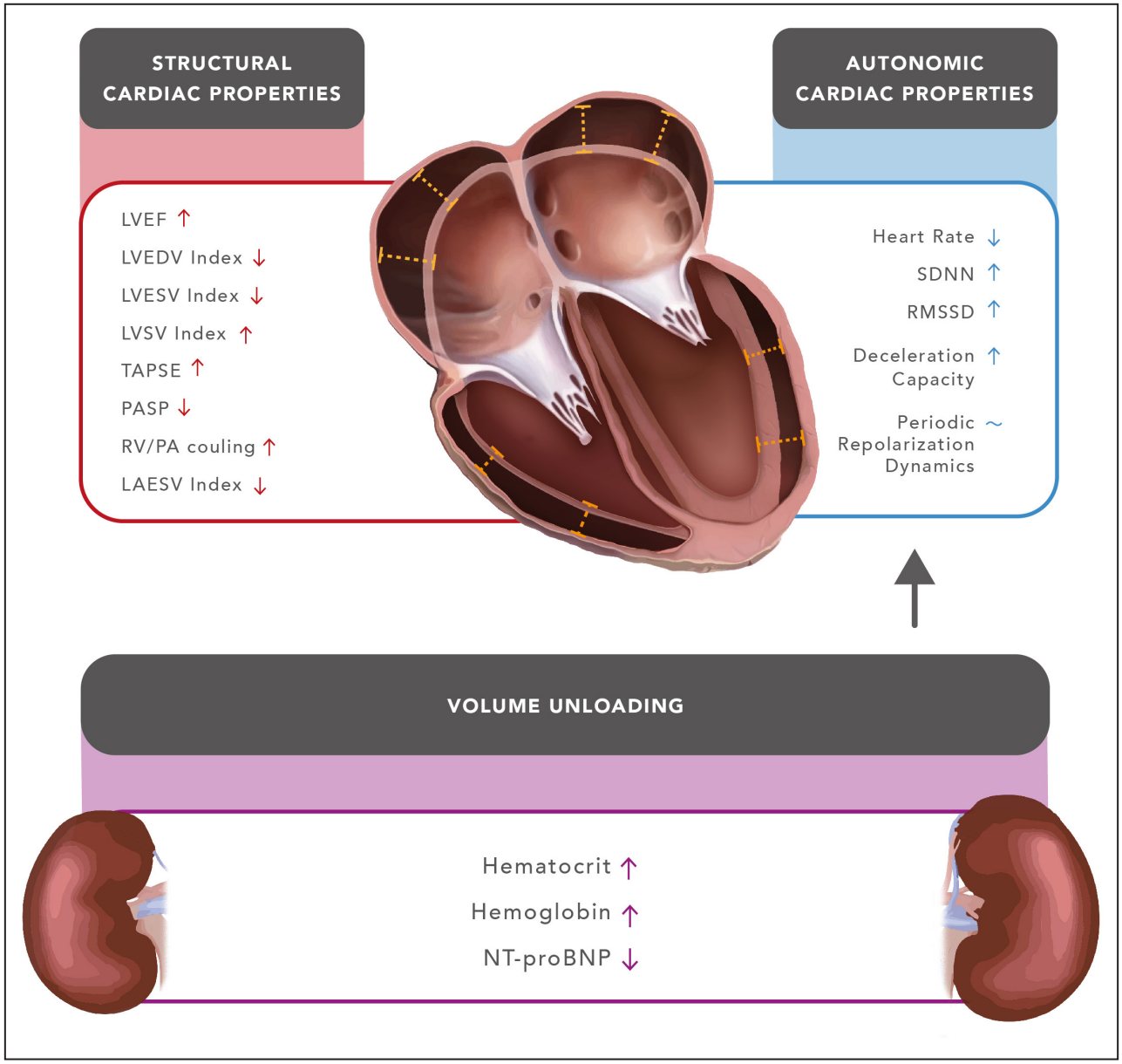

Figure 3. Schematic representation of structural and autonomic cardiac effects of 3-month ARNI therapy.
LAESV indicates left atrial end-systolic volume; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; NT-proBNP, N-terminal pro B-type natriuretic peptide; PASP, pulmonary artery systolic pressure; RMSSD, mean square of differences between consecutive R-R intervals; RV/PA, right ventricular/pulmonary arterial coupling; SDNN, SD of normal-to-normal intervals; and TAPSE, tricuspid annular plane systolic excursion.

suggest an increase in parasympathetic activity and possibly restoration of sympatho-inhibitory influences. This effect may be baroreceptor mediated against the background of an increased stroke volume (LV stroke volume index).[37,38]

Consistent with our results, the PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure) Trial demonstrated that ARNI therapy resulted in significant reductions in LVEDV index, LVESV index, and left atrial volume index (and thus volume unloading) over a 12-month period.[39]

The sympathetic inhibition postulated in our hypothesis is supported by the results of Bunsawat et al. who demonstrated a significant decrease in muscular sympathetic nerve activity (a nonpharmacological measure of baroreflex sensitivity[40]) in patients with HFrEF after 2 months of ARNI therapy.[41] In addition, Lorgis et al.

Table 3. Correlation Analysis Regarding Relationship Between Autonomic Function, LVEF, and NT-proBNP

	Pearson correlation	LVEF	Pearson correlation	NT-proBNP
SD of normal-to-normal intervals	0.09	*P*=0.55	−0.45	*P*=0.002
mean square of differences between consecutive R-R interval	0.125	*P*=0.40	−0.37	*P*=0.011
Heart rate	−0.08	*P*=0.58	−0.39	*P*=0.008
Deceleration capacity	0.03	*P*=0.82	−0.18	*P*=0.23
NT-proBNP	−0.20	*P*=0.17	/	/

LVEF indicates left ventricular ejection fraction; and NT-proBNP, N-terminal pro B-type natriuretic peptide.

showed a significant correlation between impaired HRV and elevated NT-proBNP levels in patients post infarction.[42]

However, it must be considered, that the overall advantage of ARNI-induced improvement in cardiac function is most likely due to a complex interplay of multiple interrelated mechanisms exhibited by its components sacubitril and valsartan. These may include the observed volume-unloading[39] with associated autonomic and neurohumoral remodeling (NT-proBNP reduction[39,43] and renin-angiotensin-aldosterone-system inhibition[44]) as well as reverse cardiac remodeling including reduction in cardiac fibrosis, hypertrophy, and inflammation.[27,45–47] In this context the advantage of ARNI-induced volume unloading over diuretics may be explained as chlortalidone and furosemide for example, have been shown to activate renin-angiotensin-aldosterone-system and increase sympathetic nerve activity, both of which are known to play a central role in HFrEF progression.[48–50]

Periodic Repolarization Dynamics and Power Spectral Density

There may be several reasons for the absence of significant PRD changes. On the one hand, PRD is not a simple measure of sympathetic activity but most likely reflects sympathetic influence on LV myocardium, that is, a combination of stimulus (sympathetic activity) and substrate (scar, fibrosis, inhomogeneous innervation). On the other hand, the aforementioned ventricular substrate for PRD (eg, fibrosis) remains stable between baseline and follow-up.[33,39,42,51] In this context, patients with nonischemic dilated cardiomyopathy, who presumably have less myocardial scar tissue compared with patients with ischemic cardiomyopathy, showed a numerical greater decrease in PRD under resting conditions (7.4 to 5.2 deg^2 versus 5.1 to 4.2 deg^2, Figure S1). However, the difference is not significant (*P*=0.90) and must be interpreted with caution.

Another method for estimating autonomic cardiac tone is power spectral density analysis (Table S2). However, power spectral density provides an imprecise approximation of autonomic tone and is significantly affected by respiratory rate.[21,52] Interpretation of power spectral density may be challenging, because the low-frequency domain (0.04–0.15 Hertz) does not—as is often assumed—represent sympathetic nervous system, but is composed of approximately half sympathetic and half parasympathetic influences. In contrast, the high-frequency domain (0.15–0.40 Hertz) does not represent vagal tone but indicate vagal modulation of the HR.[21] The complex composition of low frequency and high frequency, including the nonlinear relationship between sympathetic and parasympathetic nervous systems, indicate that low frequency/high frequency ratio does not reflect an adequate measure of sympathetic-parasympathetic balance.[52] Given these limitations and uncertainties, DC and PRD may represent preferable parameters.[10,13,14]

Previous Studies on Autonomic Tone With ARNI Therapy

There are only few studies investigating the influence of ARNI on CANS and results are heterogeneous. Such divergence may result from individual heterogeneity of CANS but also from small case numbers included in previous studies.[53,54] Whereas Pastor-Pérez et al. were unable to detect any difference in autonomic cardiac tone 3 months after initiation of ARNI therapy in their cohort of 21 patients, we demonstrated highly significant results for a particularly parasympathetic modulation of CANS. Reasons for the differences to our results despite similar ARNI doses may include the limited number of patients studied, the healthier collective in terms of autonomic function (baseline SDNN 42 milliseconds versus 25 milliseconds), and the high proportion of patients (50%) on amiodarone, which is known to possibly induce a suppression of HRV.[54,55]

In agreement with our results, Giallauria and colleagues found a significant improvement in HR recovery in 134 patients after 12 months of ARNI therapy.[54] HR recovery within the first minute after exercise is primarily seen as an expression of parasympathetic influences[56] and is a strong independent predictor of all-cause mortality when restricted.[57]

Limitations

Given the exploratory nature of this study, the sample size was small. HRV does represent an indirect estimate of cardiac autonomic function with limitations driven by influence of respiration and changes in HR. The precise mode of how ARNI affects HRV parameters cannot be addressed by this study and may be confounded by concomitant improvements in cardiovascular status. In addition, confounding influences on autonomic system at baseline and follow-up, which could have partially distorted the results, cannot be completely ruled out. Although we tried to reduce these to a minimum by standardizing the measurements as much as possible, coffee consumption, anxiousness/excitement, and physical exertion may have had an influence despite the 10-minute rest phase before initiation of the measurement. Furthermore, 88% of the patients included were male and the results may therefore not apply to women.

CONCLUSIONS

Initiation of ARNI therapy modulates CANS with evidence of parasympathetic activation, an effect most likely induced by cardiac volume unloading. The combination of improvements in structural and autonomic properties may provide explanation for the beneficial effects observed with ARNI in HFrEF.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S2
Figures S1–S2

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