Increased concentrations of bioactive adrenomedullin subsequently to angiotensin-receptor/neprilysin-inhibitor treatment in chronic systolic heart failure

Henrike Arfsten1 | Georg Goliasch1 | Philipp E. Bartko1 | Suriya Prausmüller1 | Georg Spinka1 | Anna Cho1 | Johannes Novak1 | Helmuth Haslacher1 | Guido Strunk2 | Joachim Struck3 | Martin Hülsmann1 | Noemi Pavo1

1Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Vienna, Austria
2Complexity Research, Vienna, Austria
3Sphingotec GmbH, Hennigsdorf, Germany

Correspondence
Martin Hülsmann MD, Department of Cardiology, Medical University of Vienna, Austria, Waehringer Guertel 18-20, 1090, Vienna, Austria. Email: martin.huelsmann@meduniwien.ac.at

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Aims: The clinically investigated rationale for neprilysin (NEP)-inhibition by angiotensin-receptor-NEP inhibitor (ARNi) therapy is to induce elevations in endogenous natriuretic peptides. NEP, however, cleaves a broad spectrum of substrates, which partially hold significant implications in heart failure with reduced ejection fraction (HFrEF). The effect of NEP inhibition on these peptides has not been investigated thoroughly. This study explored the response of adrenomedullin (ADM) regulation to the initiation of ARNi.

Methods: Seventy-four patients with stable HFrEF and initiation of ARNi were prospectively enrolled, 67 patients on continuous angiotensin-converting-enzyme inhibitor (ACEi)/angiotensin-receptor blocker (ARB) therapy served as control. Plasma bioactive-ADM (bio-ADM), mid-regional-pro-ADM (MR-proADM), B-type natriuretic peptide (BNP) and N-terminal-pro-BNP (NT-proBNP) were determined at baseline, short-term, 1-year and 2-year follow up.

Results: Following ARNi initiation both bio-ADM and MR-proADM concentrations were significantly increased at early and long-term follow up (bio-ADM [pg/mL]: 26.0 [interquartile range (IQR): 17.7–37.5] vs. 50.8 [IQR: 36.5–78.1] vs. 54.6 [IQR: 42.0–97.1] vs. 57.4 [IQR: 48.5–161.6]; MR-proADM [nmol/L]: 0.87 [IQR: 0.64–1.12] vs. 1.25 [IQR: 0.93–1.79] vs. 1.42 [IQR: 0.95–1.90] vs. 1.60 [IQR: 1.12–2.46], P < .0001 for all). The ratios bio-ADM/MR-proADM and BNP/NT-proBNP increased during ARNi-therapy proving improved availability of bioactive peptides. The proportional increase of bio-ADM markedly exceeded BNP increase. Patients converted to ARNi showed similar biomarker patterns irrespective of baseline renin–angiotensin system blocker therapy, i.e. ACEi or ARB (P > .05 for all), indicating that activation of the ADM-axis arises particularly from NEP inhibition.

The authors confirm that the PI for this paper is Martin Hülsmann MD and that he had direct clinical responsibility for patients.

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Conclusion: The significant increase of MR-proADM and bio-ADM together with an elevated bioADM/MR-proADM ratio suggest both enhanced formation and reduced breakdown of bioactive ADM following the initiation of ARNi. Activation of the ADM-axis represents a so far unrecognized effect of ARNi.

Keywords: adrenomedullin, angiotensinreceptor-neprilysin inhibitor, bioactive adrenomedullin, heart failure, neprilysin

1 INTRODUCTION

Sacubitril/valsartan, the first angiotensinreceptor-neprilysin (NEP) inhibitor (ARNi), introduced NEP inhibition (NEPi) as a novel mechanism for routine heart failure (HF) therapy.\(^1,2\) The only clinically tested hypothetical rationale for NEPi is the increase of endogenous natriuretic peptide (NP) levels by blocking the proteolytic inactivation of NP, including B-type NP (BNP). NEP, however, catalyses the degradation of >50 putative substrates including adrenomedullin (ADM).\(^3\)

ADM is a regulatory peptide with prominent vasodilating properties.\(^4,5\) It protects the vasculature by restoring impaired vascular integrity and exerts positive inotropic, as well as antifibrotic, angiogenic, anti-inflammatory and natriuretic effects.\(^6,7\) Increased plasma ADM levels in HF are associated with congestion and worse prognosis suggesting that the increase of ADM is a consequence of a compensatory response analogously to the effects of BNP.\(^6,8\)–\(^10\) Manipulation of the ADM-system is believed to be a promising therapeutic strategy in HF.\(^9\) Mid-regional pro-ADM (MR-proADM), a stable fragment of the precursor molecule, was commonly used as a surrogate for ADM actions.\(^4,6\) Recently, the direct measurement of bioactive ADM (bio-ADM) became available, which aids further characterization of ADM regulation.

Although NP levels have been investigated in patients receiving ARNi therapy, no data are available on long-term effects especially regarding alternative biological pathways. Our study aimed to investigate the proposed potentiation of ADM, reflected by plasma bio-ADM and MR-proADM levels, in direct comparison to BNP and N-terminal pro-B-type NP (NT-proBNP), in order to consider additional mechanisms contributing to the effects of ARNi therapy in HF patients.

What is already known about this subject

- The underlying mechanism of action of neprilysin (NEP) inhibition by angiotensinreceptor-NEP inhibitors in patients with heart failure remains elusive.
- Sacubitril/valsartan markedly reduces plasma NEP activity, accompanied by increased concentrations of natriuretic peptides.

What this study adds

- NEP inhibition results in a robust activation of the adrenomedullin (ADM) axis.
- Proportional increase in bio-ADM exceeds B-type natriuretic peptide elevation, suggesting the involvement of bio-ADM in the mechanisms of angiotensinreceptor-NEPinhibitor therapy.
- Testing more specific interventions aiming to increase bio-ADM levels may be considered for heart failure with reduced ejection fraction.

2 MATERIALS AND METHODS

2.1 Study population

This study is a nonrandomized observational trial based on a prospective registry linked to a biobank at the Vienna General Hospital. The study protocol complies with the Declaration of Helsinki and was approved by the local ethics committee of the Medical University of Vienna. Written informed consent was obtained from all study participants.

Consecutive patients with stable chronic HF with reduced ejection fraction (HFrEF)\(^1\) in whom ARNi therapy was initiated were enrolled between February 2016 and November 2018. Patients on continuous therapy with angiotensin-converting-enzyme inhibitor (ACEi) or angiotensin-receptor blocker (ARB) were enrolled as controls between February 2016 and June 2017. ARNi patients had to have a baseline sample and at least 1 available blood sample within 18 months after the initiation of ARNi, control patients had to have baseline as well as 1-year and 2-year follow-up (FUP) samples as defined later. The decision for the initiation of ARNi therapy was made according to the HF guidelines and the treating physician’s discretion.\(^1\) ARNi therapy was up-titrated to the maximum tolerated dose within 2 weeks. Comorbidities, traditional risk factors and medical therapy were recorded. Patients were followed-up as clinically appropriate.
### 2.2 Biobank and follow-up intervals

Serial venous blood sampling was performed routinely within the registry. For patients with therapy switch to ARNi, baseline samples were obtained at the day of initiation or ARNi therapy. Short-term FUP was defined as the first sample obtained after 4 weeks of therapy switch but not later than 6 months. 1-year and 2-year FUP samples were obtained at 12 ± 6 months and 24 ± 6 months. For control patients, baseline samples were chosen as the earliest samples within the registry that allowed matching of 1-year and 2-year FUP samples accordingly.

### 2.3 Laboratory analysis and biomarker assays

 Routinely available measurements were performed according to the local laboratory’s standard procedure. Detailed information on laboratory assays used are described in the online supplemental material (methods S1).

### 2.4 Study outcome measures

Plasma concentrations of bio-ADM, MR-proADM, BNP and NT-proBNP between baseline and FUP samples were compared.

### 2.5 Sample size

At the time of study initiation, no data were available on changes of NEP substrates other than BNP and NT-proBNP in response to ARNi therapy; therefore, estimation of sample size was not possible. This study included all patients at our heart failure unit in whom a transition from classical renin-angiotensin system (RAS) blockade to ARNi was conducted.

### 2.6 Data and statistical analysis

The data and statistical analysis comply with the recommendations on experimental design and analysis in pharmacology. Continuous data are presented as median and interquartile range (IQR) and categorical data as counts and percentages. The Spearman \( \rho \) correlation coefficient was calculated for bio-ADM, MR-proADM, BNP and NT-proBNP and baseline variables for all patients. Medians between groups were compared using the Mann–Whitney U-test, and the Wilcoxon test was performed for comparison between different timepoints. Fold changes of biomarkers were calculated for FUP levels compared to baseline. To assess alterations in the bio-ADM/MR-proADM and BNP/NT-proBNP ratios, linear regression analysis was performed for the respective pair of variables in different treatment groups and timepoints. For all tests, 2-sided \( P \)-values < .05 were considered to indicate statistical significance. The statistical analysis was carried out with SPSS software for Mac OS 10 operating system, Version 24.

### 2.7 Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

### 3 RESULTS

#### 3.1 Baseline characteristics

Seventy-four HFrEF patients with therapy switch to ARNi and 67 control patients on stable ACEi/ARB regimen were included in the study. The detailed baseline characteristics and outcome data for the total study cohort are displayed in Table 1. Short-term FUP samples were obtained at a median of 86 days (IQR: 46–119) after initiation of ARNi therapy and were available for 65 patients. 1-year and 2-year FUP samples were obtained at a median of 359 days (IQR: 246–418) and 639 days (IQR: 615–726) after therapy switch and were available for 53 and 25 patients, respectively. Median time interval from baseline to 1-year and 2-year FUP for control samples was 370 days (IQR: 301–392) and 722 days (IQR: 640–742), respectively.

#### 3.2 Effect of initiation of ARNi therapy on bio-ADM, MR-proADM, BNP and NT-proBNP

Correlations between bio-ADM, MR-proADM, BNP, NT-proBNP, the main baseline characteristics and HF severity were displayed as a cross table (Table 2). Figure 1 displays plasma levels of the active peptide hormones and their precursors. Bio-ADM showed a significant increase after ARNi initiation at short-term FUP and remained elevated at the 1-year and 2-year FUP (\( P < .0001 \) for all) as did MR-proADM (\( P < .0001 \) for all). NT-proBNP levels were decreased at short-term FUP and at 1-year FUP (\( P = .019; \ P = .031 \), respectively) but were again comparable to baseline at 2-year FUP. BNP levels remained unchanged at short-term and 1-year FUP but were higher compared to baseline levels at 2-year FUP (\( P = .031 \)). Controls showed comparable baseline biomarker levels to the ARNi cohort. Plasma levels of bio-ADM and MR-proADM remained unchanged when continuing therapy with classical RAS-blockade, i.e. ACEi/ARB. The exact numerical values of the biomarker levels are listed in Table S1.

Figure 2 illustrates the increase in bio-ADM and MR-proADM as fold changes at 1- and 2-year FUP respective to baseline levels for patients undergoing ARNi therapy initiation in direct comparison to the control group (bio-ADM: 2.1 [IQR: 1.7–2.8] and 2.5 [IQR: 2.0–3.6]; MR-proADM: 1.5 [IQR: 1.3–1.7] and 1.7 [IQR: 1.5–1.9] for 1- and 2-year FUP, respectively). Results for ARNi patients were
virtually unchanged when analysing the subgroup of patients with a complete dataset \( (n = 22, \text{Figure S1}) \). Moreover, changes in biomarker patterns were the same for both patients with ACEi and ARB therapy at baseline showing no in between group differences \((P > .05\) for all comparisons ARB vs ACEi, \text{Figure S2})

The relationship between the active peptides BNP and bio-ADM and their inactive precursor counterparts NT-proBNP and MR-proADM is visualized in \text{Figure 3}. The BNP/NT-proBNP and bio-ADM/MR-proADM ratios were similar between ARNi and control patients at baseline \( \text{median 0.14 [IQR: 0.10–0.20]} \) vs. \( 0.12 \text{[IQR:} \)
### TABLE 2  Correlation between bio-ADM, MR-proADM, BNP and NT-proBNP, and patients characteristics at baseline. Spearmann's correlations coefficient and levels of significance are indicated for relevant associations in a correlation table

| Biomarkers | Bio-ADM | MR-proADM | BNP | NT-proBNP | Age | BMI | SBP | HR | Creatinine | Hb | Sodium | CRP |
|------------|---------|-----------|-----|-----------|-----|-----|-----|----|------------|----|--------|-----|
| Bio-ADM    | ---     | Rₚ = .72  | Rₚ = .21 | Rₚ = .31 | Rₚ = .31 | Rₚ = .44 | Ns  | Ns | Rₚ = .44  | Rₚ = .20 | Ns     | Rₚ = .31 |
|            |         | P < .001  | P = .014 | P < .001 | P < .001 | P < .001 |     |     | P < .001  | P = .021 |       | P < .001 |
| MR-proADM  | x       | Rₚ = .38  | Rₚ = .57 | Rₚ = .46 | Ns  | Ns  | Ns  | Ns | Rₚ = .68  | Rₚ = .33 | Ns     | Rₚ = .35 |
|            |         | P < .001  | P < .001 | P < .001 |     |     |     |     | P < .001  | P < .001 |       | P < .001 |
| BNP        | x       | x         | Rₚ = .84 | Rₚ = .27 | Ns  | Ns  | Ns  | Ns | Ns         | Ns     | Ns     | Ns   |
|            |         |           | P < .001 | P = .002 |     |     |     |     |           |        |       |      |
| NT-proBNP  | x       | x         | x     | Rₚ = .31 | Ns  | Ns  | Ns  | Ns | Rₚ = .21  | Rₚ = .29 | Rₚ = .18 | Rₚ = .26 |
|            |         |           |       | P < .001 |     |     |     |     | P = .014  | P = .001 | P = .035 | P = .004 |

bio-ADM, bioactive adrenomedullin; MR-proADM, mid-regional pro-adrenomedullin; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; BMI, body mass index; SBP, systolic blood pressure; HR, heart rate; Hb, haemoglobin; CRP, C-reactive protein.
FIGURE 1  Short-term, 1-year and 2-year follow-up changes in plasma bio-ADM, MR-proADM, BNP and NT-proBNP levels after initiation of angiotensin-receptor/neprilysin-inhibitor therapy. Individual values as well as geometric mean and 95% confidence interval of serum concentrations of biomarkers are displayed. Biomarkers were compared by the Mann–Whitney U test. ns, nonsignificant with $P \geq .05$, * for $P < .05$ and **** for $P < .0001$. bio-ADM, bioactive adrenomedullin; BNP, B-type natriuretic peptide; MR-proADM, mid-regional pro-adrenomedullin; NT-proBNP, N-terminal pro-B-type natriuretic peptide

FIGURE 2  Fold changes in plasma bio-ADM, MR-proADM, BNP and NT-proBNP, levels after initiation of angiotensin-receptor/neprilysin-inhibitor therapy compared to continuous ACEi/ARB therapy. Fold changes of long-term FUP samples respective to baseline levels are displayed as geometric mean and 95% CI. Biomarker levels for each timepoint were compared by the Wilcoxon test, statistical significance is indicated. Ns for nonsignificant with $P \geq .05$, * for $P < .05$, ** for $P < .01$ and *** for $P < .001$. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; FUP, follow-up; bio-ADM, bioactive adrenomedullin; MR-proADM, mid-regional pro-adrenomedullin; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide

0.08–0.17], $P = .090$ and $31.5$(pg/mL)/(nmol/L) [IQR: 25.4–41.7] vs. $29.1$(pg/mL)/(nmol/L) [IQR: 22.2–37.5], $P = .349$). The ratios remained unchanged during FUP in the control cohort ($P = .962$ and $P = .454$ for the comparison between all timepoints). Both ratios, however, showed a significant increase in the ARNI cohort early after therapy initiation and remained elevated at long-term FUP (BNP/NT-proBNP: median 0.14 [IQR: 0.10–0.20] vs. 0.24 [IQR: 0.17–0.34], $P < .001$ and vs. 0.26 [IQR: 0.16–0.37], $P < .001$; bio-ADM/MR-proADM (pg/mL)/(nmol/L): 31.5 [IQR: 25.4–41.7] vs. 44.0 [IQR: 29.2–63.7], $P < .001$ and vs. 43.3 [IQR: 31.2–71.6], $P < .001$). Correlations between BNP and NT-proBNP as well as bio-ADM and MR-proADM remained significant during ARNi therapy ($R = .84$, $R = .83$, $R = .89$ and $R = .80$; $P < .001$ for all and $R = .73$, $R = .72$, $R = .78$ and $R = .81$; $P < .001$ for all at baseline, short-term, and 1- and 2-year FUP).
DISCUSSION

This is the first study investigating the long-term behaviour of ADM in HFrEF patients as a response to ARNi. The main findings are that: (i) circulating levels of bio-ADM and MR-proADM show a marked increase early after ARNi therapy initiation, remaining elevated at long-term FUP; (ii) the proportional increase of ADM exceeds reported changes in BNP; and (iii) compared to ACEi/ARB, ARNi results in an increased ratio of active-peptide/inactive-precursor-fragment for both the BNP- and the ADM-system, reflecting the stabilizing effect of NEPi on the bioactive peptides.

In HF, one hypothesis for the mechanism of action of NEPi is to increase NP levels, including BNP, by blocking their inactivation. The PARADIGM-HF trial (Prospective comparison of ARNi with ACEi to Determine the impact on Global Mortality and morbidity in Heart Failure) showed a modest increase in BNP levels accompanied by a decrease in NT-proBNP at 8–10 weeks. A similar dynamic course could be confirmed with our data. However, NEP cleaves a broad spectrum of peptides; thus, it was suggested that the net effect of NEPi would be more complex depending on the relative dominance of the respective substrates. The affinity of NEP to ADM is assumedly even higher than to BNP. While BNP increased by 20% from baseline levels in the PARADIGM-HF cohort, concentrations of bio-ADM and MR-proADM nearly doubled and remained stable over 2 years after the initiation of ARNi in our study. These changes were independent from baseline therapy, i.e. ACEi or ARB, supporting the theory that the activation of ADM is solely based on the introduction of NEPi. Neutral effects of RASI on ADM have also been reported in healthy subjects. An association between the excess of the increase of bio-ADM and resulting clinical benefits cannot be deduced from our data, leaving it by an observation, similarly to BNP. Increased plasma levels of the ADM precursor fragment MR-proADM are associated with worse prognosis in HF and renal disease. Bio-ADM was determined for cohorts with acute HF and sepsis and was equally related with worse outcomes. Suppression of ADM contributes to increased vascular permeability and altered endothelial repair in animal models and in vitro in cultured human veins. First in human studies proved this concept with an ADM antibody in sepsis. The preservation of endothelial integrity and influence on fluid balance might explain the important role of ADM in HF, where volume challenge, vascular leakage and formation of interstitial oedema are crucial. Recently, bio-ADM level was shown to be a strong predictor of fluid overload in new-onset or worsening HF, proposing bio-ADM as a marker of congestion. Besides its vasoactivity, effects of ADM in the cardiovascular system include positive inotropy, inhibition of cardiomyocyte hypertrophy as well as natriuretic, angiogenic and anti-inflammatory properties. Intravenous infusion of ADM results in sustained increase in cardiac output, reduction of vascular resistance and enhanced creatinine clearance in experimental models of HF.

![FIGURE 3](image-url)
The increase in MR-proADM levels reflect an upregulation of ADM production. The rise of the bio-ADM/MR-proADM ratio indicates an additional increase in the availability of biologically active ADM per precursor molecule, probably attributable to a mitigated degradation of ADM by NEP. ADM upregulation seems to be the result of a combinatory effect of NEPi with slower degradation of bio-ADM (direct effect) and an enhanced production of its precursor molecule (indirect effect). In contrast, the elevation of the BNP/NT-proBNP ratio seems to be mainly driven by a reduction of NT-proBNP, i.e. reduced formation of BNP, as a result of clinical improvement and reduced distension of the left ventricle. The bidirectional effect of reduced degradation combined with a decreased production leads to an only modest increase in BNP plasma levels.

In addition, the investigation of more specific pharmacological interventions leading to increased plasma bio-ADM levels, such as the application of the non-neutralizing ADM-binding antibody adreizinumab, would be useful and should be pursued in HF therapy.7,25

5 | CONCLUSION

ARNi therapy results in a significant upregulation of the ADM system with an early increase of both plasma MR-proADM and bio-ADM levels as well their ratio bio-ADM/MR-proADM. The findings suggest both an enhanced bio-ADM formation and an augmented availability of the bioactive peptide as a consequence of NEPi. This is the first description of the long-term behaviour of the NEP substrate ADM during initiation of ARNi therapy in HF patients. The ARNi mediated direct and indirect increase of the ADM axis represents an additional unreported mechanism of ARNi in patients with chronic systolic heart failure.

6 | LIMITATIONS

The reported findings are of preliminary nature and do not allow an interpretation of clinical benefits in relation to ADM increase, but might stimulate further research and discussion about the involvement of ADM in ARNi therapy. The relatively small sample size is not suitable for further statistically sound subgroup analysis and outcome measures. The investigation of larger cohorts are currently on their way giving rise to a more profound mechanistic understanding.30

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COMPETING INTERESTS

Joachim Struck is employed by sphingotec GmbH, a company, which commercializes and has patent rights in several of the assays used in this study (bio-ADM).

CONTRIBUTORS

Conceptualization: N.P., H.A., M.H.; methodology: N.P., H.A., J.S., G.G., M.H.; validation, N.P., H.A., G.G., M.H.; formal analysis, N.P., H.A., G. St., G.G.; investigation, N.P., H.A., G.G., P.E.B., S.P., G.Sp., A.C., J.N., H.H., J.S., M.H.; resources, M.H., N.P.; data curation: N.P., H.A., G.G., A.C., J.N.; writing—original draft preparation, H.A., N.P.; writing—review and editing, G.G., P.E.B., S.P., G.Sp., A.C., J.N., H.H., G.St., J.S., M.H., N.P.; visualization, N.P., H.A.; supervision N.P., M.H.; project administration: N.P., M.H.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Henrike Arfsten https://orcid.org/0000-0002-5836-7759
Georg Goliasch https://orcid.org/0000-0002-6219-6104
Philipp E. Bartko https://orcid.org/0000-0001-9061-4839
Suriya Praunmüller https://orcid.org/0000-0002-6937-7979
Georg Spinka https://orcid.org/0000-0002-8029-6491
Helmut Haslacher https://orcid.org/0000-0003-4605-2503
Guido Strunk https://orcid.org/0000-0002-0607-5105
Martin Hülsmann https://orcid.org/0000-0001-7944-7363
Noemi Pavo https://orcid.org/0000-0003-3377-4507

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

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