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Diverse short-term natriuretic response in acute decompensated heart failure patients undergoing Entresto™ treatment

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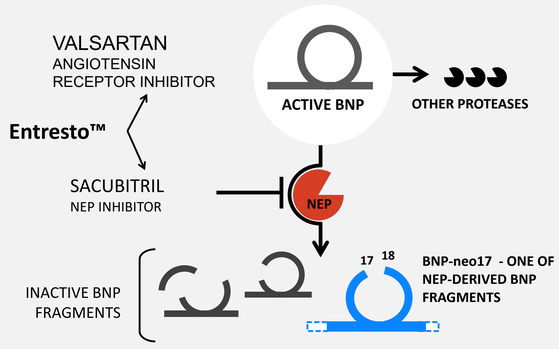
Background

A heart failure (HF) drug named Entresto™, which contains an inhibitor of protease neprilysin (NEP), was introduced into clinical practice for the treatment of chronic and acute decompensated HF (ADHF), with a more pronounced effect in the latter pathology (PIONEER-HF trial). As the bioactive form of B-type natriuretic peptide (BNP) is a known NEP substrate, Entresto™ is believed to be beneficial for HF patients as it decreases the NEP-mediated degradation of the bioactive BNP.



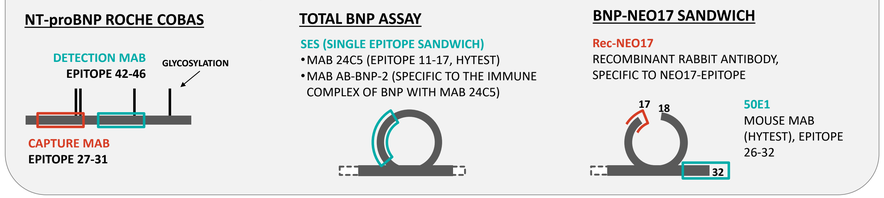
The details of this impact have still yet to be sufficiently explored. The BNP pool in the bloodstream is composed of the BNP precursor proBNP and various truncated forms of BNP, some of which retain physiological activity. This complexity makes the direct measurement of bioactive BNP in the circulation virtually impossible. We have previously described one proteolytic form, BNP-neo17, which is generated from BNP by NEP cleavage at 17-18 aar. Since BNP-neo17 is NEP-dependent, one may expect its concentration to decrease in patients undergoing Entresto™ treatment.

In the present study we evaluated the short-term dynamics of the novel BNP-neo17 form along with NT-proBNP and total BNP in ADHF patients undergoing Entresto™ treatment.

Methods

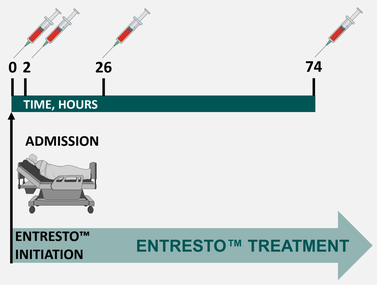
IMMUNOASSAYS

We measured NT-proBNP using a Roche Cobas e 411 analyzer, while total BNP (i.e. the sum of proBNP and mature BNP) was measured using an in-house SES-BNP immunoassay, and the BNP-neo17 form was measured using an in-house sandwich immunoassay.



In this study, total of 12 patients were hospitalized for ADHF (NYHA functional class II–IV) and they received Entresto™ two times per day for 4 days after admission. The blood of the patients was sampled at the baseline and then at 2, 26, and 74 hours after admission.

PATIENTS CHARACTERISTICS	
Diagnosis	ADHF
N	12
Age	24-76 years (median 57.5, IQR 35-70.5)
NYHA class	II - IV
LVEF	15-38% (median 26%, IQR 22-33%)

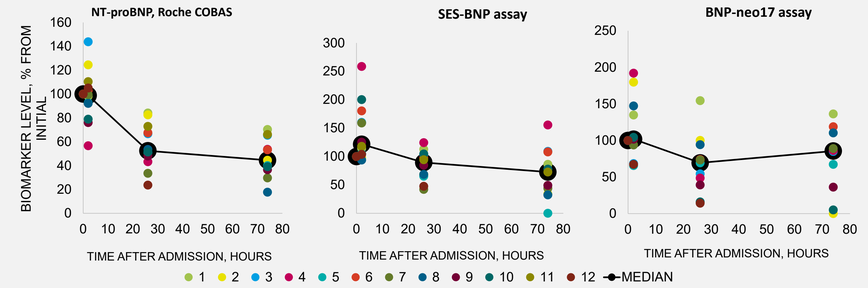


Results

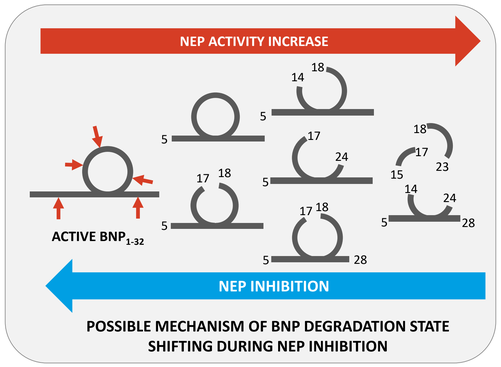
The levels of NT-proBNP, total BNP and BNP-neo17 measured at the baseline are presented in the Table below.

BIOMARKER LEVEL ON ADMISSION			
Biomarker	**Range, ng/L**	**Median**	**IQR**
NT-proBNP	508.6 – 45430	2245.0	1245.3 - 7274
Total BNP	197.4 - 27072	1923.2	987.3 – 4785.5
BNP-neo17	0 – 96.7	23.1	5.6 – 33.7

- NT-proBNP and total BNP levels exceeded the cut-off levels in all samples.
- BNP-neo17 was detected in 11 out of 12 samples.



- NT-proBNP levels decreased during treatment and they were in the range of 17.7-70.2% of the baseline concentrations after 76 hours ($P < 0.0001$).
- Total BNP did not exhibit a significant decrease; the levels after 76 hours were in the range of 32.4-155.6% of the baseline concentrations.
- BNP-neo17 exhibited no pronounced drop in concentration and it demonstrated diverse dynamics: its level varied in the range of 0-136.3% after 76 hours in other cases.



NEP cleaves BNP at multiple sites, and this leads to the formation of various truncated forms. We hypothesize that if initial NEP activity is high, then the most degraded BNP forms would be more abundant in circulation (red arrow). In this case, NEP inhibition might lead to an increase in the level of less degraded forms – such as BNP-neo17 (blue arrow). If the initial NEP activity is low, its inhibition might cause BNP-neo17 level reduction.

CONCLUSIONS

- The NEP-derived BNP-neo17 form is present in the circulation of ADHF patients.
- BNP-neo17 concentrations demonstrate variable dynamics during Entresto™ treatment, which indicates that NEP inhibition affects in different ways the proteolysis of bioactive BNP in individuals.
- Monitoring the BNP-neo17 or other NEP-derived BNP forms during Entresto™ treatment might shed more light on the perspectives of the NEP-inhibition-based therapy guidance.