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Prognostic Value and Kinetics of Soluble Neprilysin in Acute Heart Failure

A Pilot Study

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ABSTRACT

OBJECTIVES This study sought to examine the prognostic value of the soluble form of neprilysin (sNEP) in acute heart failure (AHF) and sNEP kinetics during hospital admission.

BACKGROUND sNEP was recently identified in chronic heart failure (HF) and was associated with cardiovascular outcomes.

METHODS A total of 350 patients (53% women, mean 72.6 ± 10.7 years of age) were included in the study. Primary endpoints were composites of cardiovascular death or HF hospitalizations at short-term (2 months) and long-term (mean: 1.8 ± 1.2 years) follow-up. sNEP was measured using an ad hoc–modified enzyme-linked immunosorbent assay, and its prognostic value was assessed using Cox regression analyses. In a subgroup of patients, sNEP was measured both at admission and at discharge (n = 92).

RESULTS Median admission sNEP concentrations were 0.67 ng/ml (Q1 to Q3: 0.37 to 1.29), and sNEP was significantly associated, in age-adjusted Cox regression analyses, with the composite endpoint at short-term (hazard ratio [HR]: 1.29; 95% confidence interval [CI]: 1.04 to 1.61; p = 0.02) and long-term (HR: 1.23; 95% CI: 1.01 to 1.05; p = 0.003) follow-up. In multivariate Cox analyses that included clinical variables and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentration, sNEP concentration at admission showed a clear trend toward significance for the composite endpoint at 2 months (HR: 1.22; 95% CI: 0.97 to 1.53; p = 0.09) and remained significant at the end of follow-up (HR: 1.21; 95% CI: 1.04 to 1.40; p = 0.01). At discharge, sNEP levels decreased from 0.70 to 0.52 ng/ml (p = 0.06).

CONCLUSIONS Admission sNEP concentration was associated with short- and long-term outcomes in AHF, and dynamic sNEP concentrations were observed during hospital admission. These preliminary data may be hypothesis-generating for the use of NEP inhibitors in AHF. (J Am Coll Cardiol HF 2015;3:641–4) © 2015 by the American College of Cardiology Foundation.

The enzyme neprilysin (NEP) plays a central role in neurohormonal regulation in heart failure (HF) by breaking down a plethora of vasoactive peptides (1). The extracellular domain of NEP was identified recently in ambulatory chronic HF patients as a circulating soluble form of NEP (sNEP) (2). In a large, real-life, consecutive cohort of 1,069 patients with long-term follow-up, sNEP was found to be a good pathobiological surrogate for cardiovascular mortality and morbidity (2).

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ABBREVIATIONS AND ACRONYMS

AHF = acute heart failure

ARNi = angiotensin receptor neprilysin inhibitor

CV = cardiovascular

HF = heart failure

LVEF = left ventricular ejection fraction

NEP = neprilysin

NT-proBNP = N-terminal prohormone of brain natriuretic peptide

sNEP = soluble neprilysin

In acute HF (AHF), a multitude of regulatory and counter-regulatory neurohormonal axes are acutely overexpressed (3), but no evidence is available for sNEP concentrations in AHF. Therefore, this pilot multicenter study aimed to identify the concentrations and prognostic values of sNEP in AHF and the sNEP kinetics during hospital admission.

METHODS

PATIENTS. From May 2008 to December 2013, 350 patients (mean 72.6 ± 10.7 years of age) admitted for AHF were consecutively included in the study. Inclusion criteria and blood sample collection descriptions have been described elsewhere (4,5). All participants provided written informed consent, and the local ethics committees approved the study. Primary outcomes were a composite of cardiovascular death or HF hospitalization at 2 months and at the end of follow-up.

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Human NEP concentrations were measured using a modified sandwich immunoassay (human NEP/Cd10 enzyme-linked immunosorbent assay [ELISA] kit; product no. SK00724-01, lot no. 20112070; Aviscera Biosciences, Santa Clara, California) with previously reported ad hoc modifications to improve the analytical sensitivity of the method (2). Intra- and interassay coefficients of variation were 3.7% and 8.9%, respectively.

STATISTICAL ANALYSIS. Categorical variables were expressed as percentages. Continuous variables were expressed as mean ± SD or medians (quartiles [Q]1 to Q3) according to normal or nonnormal distributions. Normal distribution was assessed with normal Q-Q plots. Values for sNEP and N-terminal prohormone of brain natriuretic peptide (NT-proBNP) concentrations were log-transformed, and 1 SD was used to calculate the hazard ratio (HR). Cox regression analyses including sNEP with age as a covariate and multivariate Cox regression analyses were performed.

RESULTS

Clinical characteristics of patients are shown in Table 1. Median sNEP concentration was 0.67 ng/ml (Q1 to Q3: 0.37 to 1.29). At 2 months, 60 composite endpoints, 28 cardiovascular deaths, and 36 HF rehospitalizations had occurred. At the end of follow-up (mean 1.8 ± 1.2 years), 158 composite endpoints, 81 cardiovascular deaths, and 120 HF rehospitalizations had occurred. As a continuous variable in age-adjusted Cox regression analyses, sNEP concentrations were significantly associated with the composite endpoint at 2 months (HR: 1.29; 95% confidence interval [CI]: 1.04 to 1.61; p = 0.02) and at the end of follow-up (HR: 1.23; 95% CI: 1.01 to 1.05; p = 0.003). sNEP concentration was also associated with cardiovascular death at 2 months (HR: 1.38; 95% CI: 1.01 to 1.88; p = 0.04). Figure 1 shows survival-free event curves for composite endpoint at 2 months and long-term follow-up for patients with sNEP concentrations below or above the median.

In a multivariate Cox regression analyses that included clinical variables (age, sex, cause of ischemia of HF, left ventricular ejection fraction [LVEF], hemoglobin and creatinine concentrations) and NT-proBNP values, sNEP showed a clear trend toward significance for the composite endpoint at 2 months (HR: 1.22; 95% CI: 0.97 to 1.53; p = 0.09). In the long-term follow-up analysis, if treatment was not incorporated in the model, both sNEP and NT-proBNP were independent predictors of the composite endpoint (p = 0.015 and p = 0.006, respectively). However, when treatment with beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, and mineralocorticoid receptor antagonists were also incorporated in the model, sNEP remained significant at the end of follow-up (HR: 1.21; 95% CI: 1.04 to 1.40; p = 0.01), but NT-proBNP lost its prognostic significance for the combined endpoint (HR: 1.19; 95% CI: 0.96 to 1.47; p = 0.12).

In a small sample of 92 patients, sNEP was also measured at discharge. In these patients, the median value decreased from 0.70 ng/ml at admission to 0.52 ng/ml at discharge (p = 0.06). We did not find significant differences between patients

TABLE 1 Demographic and Clinical Characteristics at Baseline and Treatments During Follow-Up

	Total Cohort (N = 350)
Age, yrs	72.6 ± 10.7
Females	186 (53.1)
Ischemic events as the cause of HF	132 (37.7)
LVEF, %	46.6 ± 16.2
Creatinine, mg/dl	1.26 ± 0.6
Hemoglobin, g/dl	12.2 ± 2.1
NT-proBNP ng/l	3,953 (1,988-8,155)
Neprilysin, ng/ml	0.67 (0.37-1.29)

Value are mean ± SD, n (%), or median (Q1-Q3).

HF = heart failure; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal prohormone of brain natriuretic peptide.