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Serum neprilysin and the risk of death in patients with out-of-hospital cardiac arrest of non-traumatic origin

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Abstract

Background: Early risk stratification remains an unmet clinical need in patients with in out-of-hospital cardiac arrest. We hypothesised that soluble neprilysin may represent a promising biomarker in patients with out-of-hospital cardiac arrest of non-traumatic origin and provide new pathobiological insight.

Methods: This pilot study was a biomarker analysis from the Heidelberg Resuscitation Registry. Serum soluble neprilysin levels on admission were measured in 144 patients with successful return of spontaneous circulation after out-of-hospital cardiac arrest of non-traumatic origin. The primary endpoint was time to all-cause mortality. KM Event Rates are reported. Cox models were adjusted for age, bystander resuscitation, initial ECG rhythm, baseline estimated glomerular filtration rate, baseline lactate, left ventricular function at baseline, and targeted temperature management.

Results: In total, 90 (62.5%) patients died over a follow-up of at least 30 days. Soluble neprilysin correlated weakly with high-sensitivity troponin T (r=0.18, P=0.032) but did not correlate significantly with estimated glomerular filtration rate (r=−0.12) or lactate (r=0.11). Patients with elevated soluble neprilysin levels on admission were at significantly higher risk of all-cause mortality (Q4 69.1% vs. Q1 48.4%). After multivariable adjustment, soluble neprilysin in the top quartile (Q4) was significantly associated with all-cause mortality (Q4 vs. Q1: adjusted hazard ratio 2.48 (1.20–5.12)). In an adjusted multimarker model including high-sensitivity troponin T and high-sensitivity C-reactive protein, soluble neprilysin and high-sensitivity troponin T remained independently associated with all-cause mortality (soluble neprilysin: adjusted hazard ratio 2.27 (1.08–4.78); high-sensitivity troponin T: adjusted hazard ratio 3.40 (1.63–7.09)).

Conclusion: Soluble neprilysin, measured as early as on hospital admission, was independently associated with all-cause mortality in patients with out-of-hospital cardiac arrest of non-traumatic origin and may prove to be useful in the estimation of risk in these patients.

Keywords

Out-of-hospital cardiac arrest, biomarker, neprilysin

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Background

Post-cardiac arrest management can be challenging and despite substantial advances in medical treatment mortality remains high.[1] Pathobiological processes caused by ischaemia and reperfusion following return of spontaneous circulation (ROSC) are often summarised as post-cardiac arrest syndrome and are characterised by myocardial dysfunction.[1–4] Thus, in addition to disease-specific interventions,

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early haemodynamic stabilisation is paramount in these patients. Furthermore, (very) early risk stratification remains an unmet need in patients with out-of-hospital cardiac arrest (OHCA). In this context, biomarkers are minimally invasive tools that may carry prognostic information, help to gain insight into pathophysiological processes, and/or assist in clinical decision making.[5]

The overwhelming results of the Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibition (ARNI) with ACE-Inhibition to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM–HF) trial which showed a 20% reduction of total mortality in angiotensin receptor–neprilysin inhibitor treated patients (vs, enalapril) with heart failure and reduced ejection fraction nourished the rationale of a potential prognostic role of soluble neprilysin (sNEP) in these patients.[6,7] Despite the identification of neprilysin in 1973,[8] sNEP levels have emerged as promising biomarkers only relatively recently.[9,10] Neprilysin is a membrane-bound endopeptidase, located in several different tissues such as heart, lung, brain, kidney and vasculature, and plays an important role in neurohormonal regulation and maintenance of fluids by degrading and cleaving vasoactive peptides.[11–13] In light of these observations, we sought to study the potential prognostic role of sNEP and to understand better the pathobiology in patients with OHCA of non-traumatic origin in the present pilot study.

Materials and methods

Patient population

The present analysis was a biomarker study of the prospective ongoing Heidelberg Resuscitation Registry. The protocol was approved by the institutional review board (S388-2011), and written informed consent was obtained from all patients or their legal representatives. The Heidelberg Resuscitation Registry is a prospective registry enrolling all patients after successful ROSC after a non-traumatic cause of OHCA who were admitted to the intensive care unit of the University Hospital of Heidelberg.[14] Patients with available blood samples at baseline who were included in a consecutive fashion between June 2013 and February 2016 were considered for the present analysis. All patients were treated according to standard operating procedures based on current guidelines and literature. Targeted temperature management (TTM) was performed by use of an endovascular cooling device (Coolgard 3000/ICY catheter; Zoll Medical Corp., USA) and a target temperature of 33°C was maintained for 24 hours. Patients not treated with TTM using an endovascular cooling device were externally cooled using basic tools such as ice packs and cold saline solution targeted to maintain a temperature at 36°C. An endovascular cooling device was not implemented in the case of unavailability of a device at the time of initial presentation or contraindications (e.g. severe bleeding, or regained consciousness prior to presentation).

Laboratory assessment and biomarker testing

The protocol specified blood samples to be obtained on admission in serum-separating and ethylenediamine tetraacetic acid (EDTA)-anticoagulated plastic tubes; serum and plasma were isolated within 60 minutes of sample acquisition and then stored at −80°C until measurement. sNEP concentrations were measured at the first thaw using the Human Neprilysin DuoSet ELISA research kit (product number DY1182; R&D Systems) in serum samples. All biomarker testing was performed by personnel blinded to clinical outcomes in the affiliated research laboratories of the University Hospital Heidelberg.

Measurement of high-sensitivity troponin T (hsTnT) and high-sensitivity C-reactive protein (hsCRP) was part of the department-specific standard operating procedure in OHCA patients, and was measured in the clinical core laboratory of the University Hospital of Heidelberg. Concentrations of hsTnT were measured with an electrochemiluminescent immunoassay (Roche Diagnostics). The lower limit of detection of the assay is 3 ng/L.[15,16] Concentrations of hsCRP were measured with an enhanced immunonephelometric assay (Siemens Healthineers) with a lower level of detection of 0.015 mg/dL and a functional sensitivity of 0.03 mg/dL. Measurement of NT-pro brain natriuretic peptide (BNP) on admission was not routinely performed and is therefore missing in 78 patients (54.2%) at baseline. Plasma NT-proBNP was measured using a chemiluminescent immunoassay (Siemens Healthineers). The analytic range extends from 15 to 20,000 pg/mL. The reported within-run coefficient of variation was 4.4% at a level of 96.6 pg/mL.[17]

Endpoints

The primary endpoint for this biomarker analysis was time to all-cause mortality (ACM). All patients were followed for at least 30 days. Specific causes of death were not adjudicated in the present study.

Statistical analysis

The baseline characteristics of this patient cohort stratified by biomarker quartiles were compared using the Wilcoxon rank sums test for continuous variables and the chi-square test for categorical variables. Correlations were examined using Spearman coefficients. Plasma concentrations of sNEP and all other biomarkers (hsTnT, NTproBNP and hsCRP) were categorised by quartiles. In addition, all biomarkers were modelled as continuous variables. Kaplan–Meier estimates are reported at 5 days and 30 days. Adjusted hazard ratios (HRs) were determined using a Cox proportional hazards regression model that included the following variables: age (continuous), bystander resuscitation (yes/no), initial ECG rhythm (shockable vs. non-shockable), baseline estimated glomerular filtration rate (eGFR) (modelled continuously

Table 1. Baseline characteristics for the total study population and stratified by quartiles of neprilysin (all *P* values >0.05, except for eGFR (*P*=0.024) and hsTnT (*P*=0.048)).

	Q1 (<565 pg/ml) *n*=36	Q2 (565-1105 pg/ml) *n*=36	Q3 (1105-2047pg/ml) *n*=36	Q4 (>2047 pg/ml) *n*=36	Overall
Age (median, IQR)	64.4 (49.5–74.6)	72.1 (63.6–79.8)	67.3 (57.9–77.1)	69.1 (53.8–78.8)	68.3 (56.0–77.7)
Female sex	10 (27.8%)	14 (38.9%)	5 (13.9%)	12 (33.3%)	41 (28.5%)
Bystander-initiated CPR	25 (69.4%)	22 (61.1%)	22 (61.1%)	19 (52.8%)	88 (61.1%)
Time to ROSC (min) (median, IQR)	17.5 (10.0–30.0)	20.0 (12.8– 30.0)	30.0 (15.5, 35.0)	20.0 (15.0, 30.0)	23.0 (14.5–30.0)
Shockable first monitored heart rhythm	15 (41.7%)	11 (30.6%)	16 (44.4%)	14 (38.9%)	56 (38.9%)
Cause of resuscitation of cardiac origin	25 (69.4%)	22 (61.1%)	25 (69.4%)	19 (52.8%)	91 (63.2%)
Endovascular cooling device	25 (69.4%)	23 (63.9%)	30 (83.3%)	21 (58.3%)	99 (68.8%)
eGFR (ml/min/1.73m²) (median, IQR)	62 (44–78)	42 (31–62)	53 (47–69)	48 (39–72)	52 (37–71)
hsTnT (pg/ml) (median, IQR)	79 (38–222)	106 (46–215)	201 (115–494)	158 (55–464)	124 (51–397)
hsCRP (mg/dl) (median, IQR)	9.7 (2.4–42.8)	11.0 (2.0–32.2)	2.5 (2.0–10.8)	8.0 (2.0–21.0)	6.5 (2–27)
NT-proBNP (pg/ml) (median, IQR)	1773 (367–2923)	2684 (789–17824)	1722 (278–5273)	819.5 (299–2052)	1774 (348–5572)
Lactate (mg/dl) (median, IQR)	6.7 (4.0–12.3)	7.7 (4.2–10.5)	8.9 (6.4–11.3)	10.0 (6.3–12.2)	8.7 (4.8–11.7)

eGFR: estimated glomerular filtration rate; hsTnT: high-sensitivity troponin T; IQR: interquartile range; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; hsCRP: high-sensitivity C-reactive protein; NT-proBNP: NT-pro brain natriuretic peptide.

using the CKD–EPI equation), lactate at baseline (continuous), left ventricular function at baseline (described as normal or mildly impaired or ejection fraction ⩾45% vs. moderately to severely or ejection fraction <45%), and TTM (yes/no). In addition, a multimarker model including hsTnT and hsCRP was fitted. Due to the large amount of missing values for NT-proBNP concentrations, further adjustment for NT-proBNP was only performed in the form of sensitivity analyses. To explore the relationship between sNEP at baseline and ACM, we fitted adjusted Cox models with sNEP concentrations entered as natural splines. The degrees of freedom were chosen according to the Akaike information criterion (AIC) using the R package 'smoothHR'.[18] All analyses were performed using R (version 3.4.3).[19] *P* values (two-tailed) less than 0.05 were considered to indicate statistical significance. Due to the exploratory nature of this analysis no adjustments for multiple testing were performed.

Results

Study population

sNEP serum levels on admission were measured in 144 patients with OHCA after successful ROSC. Of these, 41 (28.5%) were women and the median age was 68 years (interquartile range (IQR) 55–77) (Table 1). Eighty-eight (61.1%) patients received bystander-initiated CPR, and 56 (38.9%) patients had a shockable rhythm recorded at first presentation. No patient was treated or received treatment with angiotensin receptor–neprilysin inhibitors.

In total, 90 (62.5%) patients died, of which 51 (35.7%) deaths occurred due to limitation of treatment and initiation of supportive and palliative care.

Biomarker serum levels at baseline

The median and IQR of sNEP measured at baseline was 1105 pg/ml (IQR 565–2047 pg/ml). Patients with neprilysin serum levels in the lowest quartile were more likely to have higher eGFR and lower hsTnT levels but otherwise had similar baseline characteristics (Table 1). sNEP correlated weakly with hsTnT (r=0.18, P=0.032) but did not correlate statistically significantly with eGFR (r=−0.07, P=0.40), lactate (r=0.11, P=0.20), hsCRP (r=−0.12, P=0.15) or NT-proBNP (r=−0.15, P=0.22).

sNEP concentrations and ACM

sNEP levels in the top quartile (Q4) were associated with higher rates of ACM at 30 days (Q4 vs. Q1–Q3, 69.1% vs. 57.0%;) with early separating Kaplan–Meier curves (at 5 days: Q4 vs. Q1–Q3, 54.7% vs. 33.9%; Figure 1 and Supplementary Figure 1), although a clear gradient of risk was only observed for the first 5 days (Supplementary Figures 1 and 2).

After multivariable adjustment serum concentrations in Q4 were associated with a significantly higher risk of ACM (Q4 vs. Q1: adjusted HR 2.48 (95% confidence interval (CI) 1.20–5.12); Figure 2). This association was also statistically significant when sNEP was modelled as a

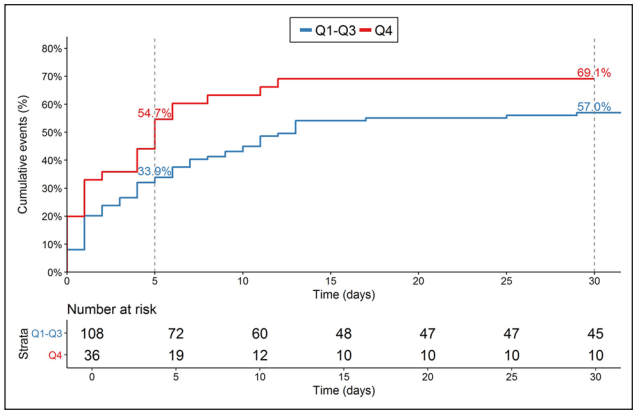

Figure 1. Kaplan–Meier curves with the respective Kaplan–Meier estimates at 5 days and 30 days for all-cause mortality stratified by the top quartile (Q4) versus Q1–Q3 of soluble neprilysin levels.

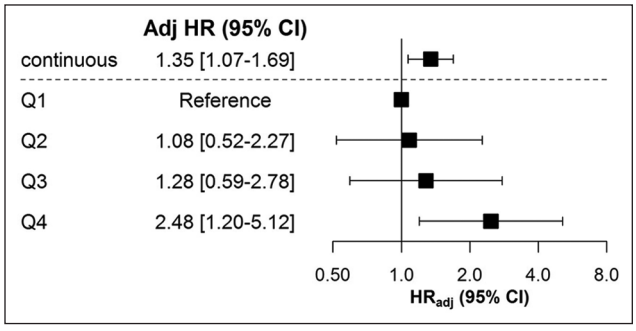

Figure 2. Adjusted hazard ratios (Adj HR) for serum neprilysin concentrations modelled as a continuous variable (per 1 standard deviation increase in log-transformed biomarker) and stratified by quartiles for all-cause death.

continuous variable (adjusted HR 1.35 (1.07–1.69) per 1 standard deviation of log-transformed biomarker). There was no interaction between sNEP levels and the risk of death by TTM versus no TTM, or any relevant subgroups such as cause of cardiac arrest, initial ECG rhythm, or left ventricular function (all P interaction >0.10).

Multimarker model

In an adjusted multimarker approach, sNEP and hsTnT in the top quartile were independently associated with ACM (Q4 vs. Q1: sNEP: adjusted HR 2.27 (95% CI 1.08–4.78); hsTnT: adjusted HR 3.40 (1.63–7.09); Figure 3). This association was robust for sNEP when all biomarkers were modelled as continuous variables (adjusted HR 1.35 (1.06–1.71) per 1 standard deviation of log-transformed biomarker). In a sensitivity analysis of a substantially smaller subgroup of 57 patients with available NT-proBNP levels, sNEP remained independently associated with ACM (adjusted HR 1.65 (1.03–2.64) per 1 standard deviation of log-transformed biomarker).

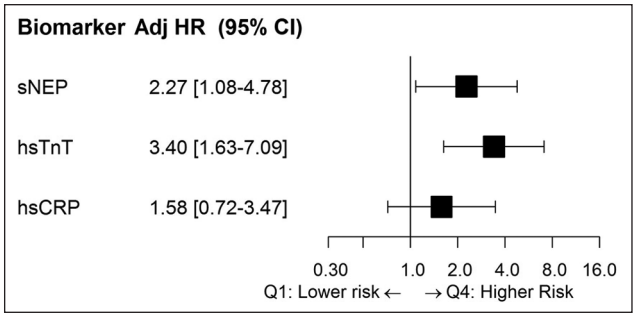

Figure 3. Adjusted multimarker model for serum neprilysin (sNEP) concentrations stratified by quartiles for all-cause death. Adj HR: adjusted hazard ratio.

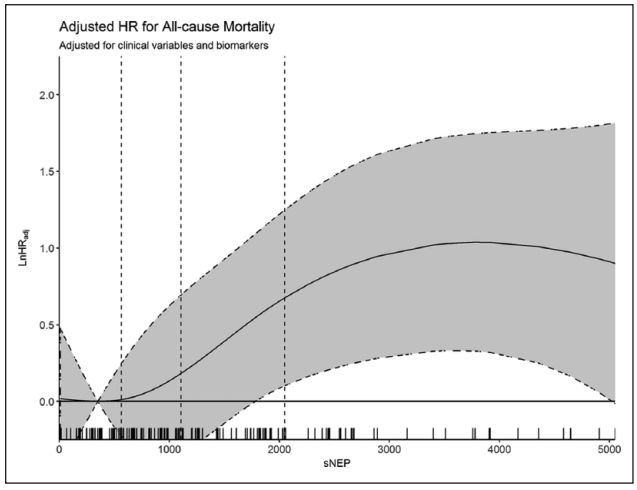

Figure 4. Estimated adjusted log-hazard ratios for all-cause mortality events in relation to continuous serum neprilysin (sNEP) levels modelled with penalised regression splines. Note the dashed vertical lines indicating the 25th, 50th and 75th percentiles. The rug plot illustrates the marginal distributions of sNEP concentration.

Relationship between sNEP and ACM

Continuous sNEP, modelled with adjusted natural smoothed regression splines, suggested that there is a consistent increase in the hazard for all-cause death from 8 to 5000 pg/ml of sNEP (Figure 4).

Discussion

The main finding of this study was that elevated sNEP concentrations were significantly associated with ACM in patients with OHCA of non-traumatic origin even after robust multivariable adjustment. This association was consistent even in the presence of markers of shock, myocardial injury, cardiac wall stress and inflammation, suggesting that sNEP concentrations may provide pathobiological insight and an independent association with prognosis in addition to these pathobiological axes.

sNEP possess enzymatic activity similar to the membrane-bound neprilysins,[12,20] but the pathways of (soluble) neprilysin-mediated degradation of bioactive peptides are complex, and not well understood. Indeed, some of the targeted peptides have opposing effects (such as vasodilation vs. vasoconstriction, or inhibition vs. activation of the renin–angiotensin–aldosterone system). Several studies indicated that sNEP levels were robustly associated with cardiovascular death and hospitalisations for heart failure independent of NT-proBNP in patients with heart failure and preserved ejection fraction (HFpEF).[9,10,21] Conflicting results on the prognostic information of sNEP have been reported for patients with HFpEF.[22,23] Noteworthy, although heavily underpowered, we did not observe any heterogeneity in our study between patients with normal or mildly impaired left ventricular function compared to patients with moderately to severely impaired left ventricular function. The ongoing Angiotensin Receptor Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction (PARAGON) trial will compare treatment with sacubitril/valsartan to valsartan in patients with HFpEF and hopefully shed light on the pathobiological differences.[24]

Myocardial dysfunction is commonly observed in OHCA patients and efforts aiming at haemodynamic stabilisation after resuscitation play an important role in post-cardiac arrest management. The early separation of the Kaplan–Meier curves may indicate that sNEP concentrations reflect critical haemodynamic alterations in the wake of cardiac arrest. However, our data do not allow us to dissect the specific cause of death. It is tempting to speculate as to whether patients with high sNEP concentrations would potentially benefit from treatment with neprilysin inhibitors/angiotensin receptor blockers, but the role of sacubitril in post-cardiac arrest patients has not been studied, and the setting of hypotension, haemodynamic instability and multiorgan failure may significantly limit its application. To reinforce the neprilysin pathway, the ongoing Comparison of Sacubitril/valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode (PIONEER–HF) trial will compare the effect of sacubitril and valsartan (LCZ696) versus enalapril on changes in NT-proBNP concentrations in patients who have been stabilised following hospitalisation for acute decompensated heart failure.[25] In addition, the Prospective ARNI vs. ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI (PARADISE–MI) trial (ClinicalTrials.gov Identifier: NCT02924727) will test the efficacy and safety of sacubitril/valsartan in patients with acute myocardial infarction and reduced ejection fraction.

Strengths and limitations

To the best of our knowledge, this is the first study examining the role of sNEP in patients with cardiac arrest. Although the present analysis benefits from a well-characterised cohort without any patients lost to follow-up, there are several limitations that should be addressed. In addition to its nature as a pilot study and thus limited sample size, this analysis stems from a single-centre observational study. Despite employing adjustments our study may be subject to residual confounding. Furthermore, we did not assess the specific causes of death, and the lack of serial biomarker measurements do not allow us to conclude on kinetics. In addition, the adjustment for NT-proBNP could only be performed in a substantially smaller subgroup due to missing values. Because of the exploratory design, no corrections for multiple testing were performed.

Conclusion

sNEP, measured as early as on hospital admission, was associated with ACM in patients with OHCA of non-traumatic origin and may prove to be useful in the estimation of risk in these patients.

Conflict of interest

TAZ reports a research grant outside the submitted work (Deutsche Forschungsgemeinschaft ZE 1109/1-1). SS, JS, FS, HAK and MRP have nothing to disclose.

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