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Proenkephalin, Renal Dysfunction, and Prognosis in Patients With Acute Heart Failure

A GREAT Network Study

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ABSTRACT

BACKGROUND Proenkephalin A (PENK) and its receptors are widely distributed. Enkephalins are cardiodepressive and difficult to measure directly. PENK is a stable surrogate analyte of labile enkephalins that is correlated inversely with renal function. Cardiorenal syndrome is common in acute heart failure (HF) and portends poor prognosis.

OBJECTIVES This study assessed the prognostic value of PENK in acute HF, by identifying levels that may be useful in clinical decisions, and evaluated its utility for predicting cardiorenal syndrome.

METHODS This multicenter study measured PENK in 1,908 patients with acute HF (1,186 male; mean age 75.66 ± 11.74 years). The primary endpoint was 1-year all-cause mortality; secondary endpoints were in-hospital mortality, all-cause mortality or HF rehospitalization within 1 year, and in-hospital worsening renal function, defined as a rise in plasma creatinine ≥26.5 μmol/l or 50% higher than the admission value within 5 days of presentation.

RESULTS During 1-year follow-up, 518 patients died. Measures of renal function were the major determinants of PENK levels. PENK independently predicted worsening renal function (odds ratio: 1.58; 95% confidence interval [CI]: 1.24 to 2.00; $p < 0.0005$) with a model receiver-operating characteristic area of 0.69. PENK was associated with the degree of worsening renal function. Multivariable Cox regression models showed that PENK level was an independent predictor of 1-year mortality ($p < 0.0005$) and 1-year death and/or HF (hazard ratio: 1.27; 95% CI: 1.10 to 1.45; $p = 0.001$). PENK levels independently predicted outcomes at 3 or 6 months and were independent predictors of in-hospital mortality, predominantly down-classifying risk in survivors when added to clinical scores; levels <133.3 pmol/l and >211.3 pmol/l detected low-risk and high-risk patients, respectively.

CONCLUSIONS PENK levels reflect cardiorenal status in acute HF and are prognostic for worsening renal function and in-hospital mortality as well as mortality during follow-up. (J Am Coll Cardiol 2017;69:56–69)

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In recent years, many advances have been made in the understanding of pathophysiology and the management of chronic heart failure (HF). However, the understanding and treatment of acute HF has remained incomplete and broadly unchanged during this period. Accordingly, prognosis remains poor, with 1-year mortality rate exceeding 25% (1). Neurohormonal activation and worsening renal function (WRF) play important roles in the pathogenesis of fluid redistribution, leading to acute decompensation (2). Use of biomarkers might help characterize different phenotypes in acute HF associated with different outcomes that may prompt specific and expedited therapies. Although activation of the natriuretic peptide system is recognized, its value in predicting death at first presentation with acute HF is suboptimal (3), and better tools are needed.

The endogenous opioids (enkephalins, endorphins, dynorphins), extensively studied in nociception and anesthesia, also have roles in cardiovascular regulation (4). Proenkephalin A (PENK) is widely expressed, and cardiac cells secrete enkephalins, which have local effects on opioid receptors. Cardiodepressive through a negative inotropic effect and lower blood pressure and heart rate (5), opioid receptors, especially the δ receptor that binds enkephalins, are widely distributed, with highest densities in the kidney (6).

The possible relationship between endogenous opioid systems and prognosis was suggested by previous studies. Data from ADHERE (Acute Decompensated Heart Failure National Registry) demonstrated that opiate administration in acute HF has been associated with poor outcomes (7). Fontana et al. (8) reported elevated met-enkephalin levels in severe acute HF compared with less severe acute HF.

In several acute disease conditions, elevated plasma levels of a PENK fragment (amino acids 119 through 159) have been associated with renal dysfunction and poor outcomes. For example, we previously demonstrated PENK to be an independent predictor of major adverse cardiac events, including death, reinfarction, and rehospitalization for HF in patients presenting with acute myocardial infarction (9). This also has been shown more recently for stable ambulatory patients with HF (10). PENK predicts acute kidney injury after cardiac surgical procedures (11) and in patients with sepsis (12), and it has been linked to death and major adverse cerebrocardiovascular events in acute stroke (13).

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In the present study, we investigated the relationship of the enkephalin system with WRF and worsening prognosis in acute HF. Renal impairment profoundly influences prognosis in HF (14), and development of acute kidney injury is common in acute HF, the so-called cardiorenal syndrome type 1 (15). We therefore examined the utility of PENK in assessing WRF in acute HF. Previous studies were hindered by the instability of met-enkephalin. we used a more recently developed assay (penKid assay, Sphingotec GmbH, Hennigsdorf, Germany) for PENK (16), with epitopes on the proenkephalin molecule that are stable in whole blood for at least 48 h, thus enabling a study of this system in acute HF. The utility of PENK for prediction of short-term and long-term outcomes and inpatient mortality was examined in combination with various clinical risk scores developed for inpatient mortality, namely ADHERE (17), GWTG-HF (Get With the Guidelines Heart Failure) (18), and OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) (19).

ABBREVIATIONS AND ACRONYMS

BNP = B-type natriuretic peptide

CI = confidence interval

eGFR = estimated glomerular filtration rate

HF = heart failure

HR = hazard ratio

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PENK = proenkephalin A

ROC = receiver-operating characteristic

SBP = systolic blood pressure

WRF = worsening renal function

METHODS

Three cohorts of unselected patients with acute HF who presented with acute dyspnea to the emergency department of the participating university hospitals in 3 countries (United Kingdom, France, and Switzerland) were recruited. Acute HF was defined, according to the guidelines of the European Society of Cardiology (20), as progressive worsening or new-onset of shortness of breath, along with clinical signs of pulmonary or peripheral edema and elevated jugular venous pressure requiring intensification of diuretic and/or vasodilator therapy. Inclusion was independent of renal function, although patients with

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