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Adaptive cardiovascular hormones in a spectrum of heart failure phenotypes

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ABSTRACT

Background/objectives: In heart failure (HF), activation of brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP) and adrenomedullin (ADM) is adaptive. The activation of these peptides in relation to different HF phenotypes such as HF with preserved ejection fraction (HFpEF), reduced ejection fraction (HFrEF) and after left ventricular assist device (LVAD) and heart transplantation (HTx) remains poorly characterized.
Methods: We measured and compared N-terminal (NT)-proBNP, mid-regional (MR)-proANP and mid-regional (MR)-proADM in 86 patients with HFpEF, 49 patients with HFrEF, 13 patients one year post-LVAD and 22 patients one year post-HTx. We assessed their prognostic impact using Kaplan–Meier analysis and multivariable Cox regression.
Results: In HFpEF, HFrEF, LVAD and HTx, NT-proBNP, median (inter-quartile range), was 1000 (465–2335), 3145 (1475–5190), 1430 (986–2570), and 208 (127–353) pmol/L, $p < 0.001$. MR-proANP was 313 (192–381), 449 (325–596), 276 (216–305), and 118 (96–163) pmol/L, $p < 0.001$. MR-proADM was 1.2 (0.9–1.6), 1.3 (0.9–2.0), 0.9 (0.7–1.4), and 0.7 (0.6–0.9) nmol/L, $p < 0.001$ overall and $p = 0.212$ HFpEF versus HFrEF. In both HFpEF and HFrEF, NT-proBNP and MR-proANP predicted survival free from HTx or LVAD, independent of age, gender, NYHA class and eGFR, whereas MR-proADM did not.
Conclusions: Patterns of the cardiomyocyte stress hormones NT-proBNP and MR-proANP suggest that compared to HFrEF, HFpEF may represent milder disease and LVAD and HTx may represent progressive resolution of HF severity. NT-proBNP and MR-proANP independently predicted prognosis in both HFpEF and HFrEF. In contrast, MR-proADM did not distinguish between HFpEF and HFrEF, did not predict prognosis in either, and may be more non-specific in HF.

1. Introduction

Heart failure with reduced ejection fraction (HFrEF) is well characterized and numerous interventions inhibit neurohormonal activation and improve outcomes [1]. In severe HFrEF, cardiac output is reduced and left ventricular device (LVAD) and heart transplantation (HTx) restore cardiac output and remove the stimuli for neurohormonal activation. Heart failure with preserved ejection fraction (HFpEF) is equally common as HFrEF, but is poorly understood and there is no therapy. It is unclear whether HFpEF is similar to HFrEF except for higher ejection fraction (EF) on a continuous spectrum, a distinct disorder dominated by diastolic dysfunction, or more likely, a mix of phenotypes where age-related co-morbidities, obesity, and deconditioning contribute to varying extents [2].

Activation of renin-angiotensin-aldosterone system (RAAS) and adrenergic neurohormones in HF is compensatory in the short run but maladaptive in the long run. In contrast, although the peptide hormones brain natriuretic peptide (BNP), atrial natriuretic peptide (ANP) and adrenomedullin (ADM) are risk markers in HF [3], their release is also adaptive and counteracts the RAAS and adrenergic systems. Indeed, inhibition of neprilysin, the enzyme that degrades BNP, ANP and ADM [4,5] has received recent attention for convincingly improving outcomes in HFrEF [6].

These peptides are well characterized in HFrEF, but their comparative roles in HF of different types and severity have not been examined.

Abbreviations: ADM, adrenomedullin; ANOVA, analysis of variance; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CI, cardiac index; CO, cardiac output; EDTA, ethylenediaminetetraacetic acid; EF, ejection fraction; GFR, glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTx, heart transplantation; LV, left ventricle; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MR-proADM, midregional pro-adrenomedullin; MR-proANP, midregional pro-atrial natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Failure Association; RAAS, renin angiotensin aldosterone system.

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Their activation is more accurately reflected by their stable precursor fragments N-terminal (NT) pro-BNP, mid regional (MR) pro-ANP and mid regional (MR) pro-ADM. The aim was to compare levels of and prognostic impact of NT-proBNP, MR-proANP and MR-proADM in different heart failure (HF) phenotypes.

2. Methods

2.1. Patients

This was a cross-sectional study of four patient cohorts: HFpEF (n = 86), HFrEF (n = 49), post LVAD (n = 13), and post HTx (n = 22).

Patients with HFpEF were recruited from the previously described Karolinska Rennes (KaRen) study. This was a prospective observational multicentre study characterizing patients with HFpEF [2,7]. Patients presenting acutely to the hospital with signs and symptoms of HF according to the Framingham criteria, NT-proBNP >300 ng/L and a left ventricular ejection fraction (LVEF) ≥45% were enrolled in French and Swedish centres. The KaRen biomarker study was a pre-specified substudy including patients enrolled at Karolinska University Hospital only. Of 530 patients in KaRen, 86 patients were recruited 21 May 2007–29 Dec 2011 and included in the present study. Patients returned to the hospital in stable condition 4–8 weeks after enrolment for a follow-up visit including blood sampling for biomarker analysis and echocardiography and were followed until 30 September 2012 when vital status was assessed by telephone contact or by the Swedish National Patient Register and Population Register.

Patients with HFrEF referred for advanced HF assessment or followed with existing LVAD or HTx were recruited from Karolinska University Hospital between January 2009 and February 2013. A total of 49 patients with HFrEF, 13 postLVAD and 22 postHTx were included in a cross-sectional analysis. Among the 49 HFrEF patients 13 were also included in the cross-sectional analysis one year postHTx and 4 patients one year postLVAD. Furthermore, 5 of the 13 patients with LVAD were also included in the cross-sectional analysis one year postHTx. A consistency longitudinal analysis was performed in patients with serial measurements.

All patients were studied in a stable euvolemic state. At each visit, fasting blood samples were collected. Cardiac index (CI) was determined primarily by the Fick method (thermodilution was used when Fick was not available) at right heart catheterization, and when that was not available, a non-invasive inert gas rebreathing technique (Innocor ®, Innovision, Odense, Denmark) which has been validated against Fick [8] (in HFrEF, LVAD and HTx patients) or by echocardiography (in HFpEF patients). CI obtained from echocardiography was calculated using the following formula: heart rate * (3.14 * [LV (left ventricle) outflow tract diameter / 2)]^2 * LV outflow tract velocity time integral) / body surface area. Estimated glomerular filtration rate (eGFR) was calculated using the MDRD formula [9].

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by the institution's human research committee, and all patients provided written informed consent.

2.2. Peptide measurements

Blood samples were collected in chilled EDTA tubes, immediately centrifuged at 4 °C and stored in aliquots in −70 °C until analysis. MR-proADM and MR-proANP were analysed in duplicate locally at the Karolinska Institute with an automated, commercially available flouroimmuno assay (us Kryptor, B-R-A-M-H-S, Henningsdorf/Berlin, Germany). The lower detection limit for MR-proADM was 0.05 nmol/L, functional assay sensitivity 0.25 nmol/L, and interassay coefficient of variation 20%. The lower detection limit for MR-proANP was 2.1 pmol/L, functional assay sensitivity <10 pmol/L and interassay coefficient of variation 20%. NTpro-BNP was analysed in the Karolinska University Hospital core laboratory by proBNPII (Roche Diagnostics, Bromma Sweden).

2.3. Statistics

Data are presented as median and interquartile range or as numbers and percentages. Overall comparisons between groups were performed with Fischer exact test with Monte Carlo adjustment and Kruskal–Wallis one-way ANOVA test. Differences between two groups were determined with Fischer exact test and Mann–Whitney *U* test. In longitudinal analysis, paired statistics were calculated with related-samples Wilcoxon signed rank test.

Events were analysed in HFrEF and HFpEF patients only, and were defined as death, LVAD or HTx, for both HFrEF and HFpEF. Waiting lists for HTx are long and prioritize urgent transplants, and LVAD for bridge to transplantation is implanted only urgently or semi-urgently. Thus survival was analysed free from LVAD or HTx, with Kaplan–Meier analysis based on peptide levels above or below median. To assess the independent impact of peptides on prognosis, multivariable Cox regression was performed separately in HFrEF and HFpEF for all the three peptides, with adjustment for age, gender, NYHA class, and eGFR.

All p-values were 2-sided and statistical significance was set at 0.05. Statistical analyses were performed in IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Clinical characteristics

Patient characteristics are shown in Table 1. LVAD and HTx patients were examined in a median (inter-quartile range) 12 (9–15) months after LVAD and 12 (11–13) months after HTx. Patients with HFpEF were the oldest (73 (67–79) years) and patients postHTx were the youngest (51 (46–56) years); age in HFrEF was 63 (50–67) years and postLVAD 56 (53–67) years, p < 0.001. About half of the HFpEF patients were women (51%), compared to 18% in HFrEF, 15% post LVAD and 9% post HTx, p < 0.001.

3.2. Peptide levels

Table 1 and Fig. 1 depict cross-sectional comparison of peptide levels. NT-proBNP (pmol/L) was 1000 (465–2335) in HFpEF; 3145 (1475–5190) in HFrEF; 1430 (986–2570) postLVAD; and 208 (127–353) pmol/L postHTx; p < 0.001 for overall comparison. MR-proANP (pmol/L) was 313 (192–381) in HFpEF; 449 (325–596) in HFrEF; 276 (216–305) postLVAD; and 118 (96–163) postHTx, p < 0.001. MR-proADM (nmol/L) was 1.2 (0.9–1.6) in HFpEF; 1.3 (0.9–2.0) in HFrEF; 0.9 (0.7–1.4) postLVAD; and 0.7 (0.6–0.9) postHTx, p < 0.001 overall and p = 0.212 HFpEF versus HFrEF. Longitudinal analyses were consistent with the cross-sectional analysis but did not reach statistical significance for all comparisons. In HFrEF to HTx, n = 13, there was a significant decline in the 3 peptides (median, interquartile range; NT-proBNP: HFrEF 1900 (1525–5090) vs. HTx 202 (129–329) pmol/L, p = 0.002; MR-proANP: HFrEF 372 (280–463) vs. HTx 106 (95–138) pmol/L, p = 0.004; MR-proADM: HFrEF 0.9 (0.7–1.3 nmol/L vs. 0.67 (0.56–0.87) nmol/L, p = 0.046)). In HFrEF to LVAD, n = 4, there were similar trends, although not statistically significant (NT-proBNP: HFrEF 4700 (2610–11,298) vs. LVAD 1214 (980–2105) pmol/L, p = 0.068; MR-proANP: HFrEF 479 (428–506) vs. LVAD 253 (226–295) pmol/L, p = 0.068; MR-proADM: HFrEF 1.6 (1.3–1.8) vs. LVAD 0.9 (0.7–1.1) nmol/L, p = 0.109). In postLVAD to post HTx, n = 5, there were again similar results, significant for NT-proBNP and MR-proANP but not for MR-proADM (NT-proBNP: LVAD 1430 (701–3360) pmol/L, HTx 242 (128–294) pmol/L, p = 0.043; MR-proANP: LVAD 224 (197–315), HTx 122 (84–161), p = 0.043, MR-