

Heart Failure: Advanced Treatments and Novel Hormonal Responses

AKADEMISK AVHANDLING

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av

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ABSTRACT

Background

Heart failure (HF) affects 2-3% of the Western population and is associated with a 1 year mortality of 20%. Despite therapeutic advances over the last decades, numerous unanswered questions remain regarding the impact of currently established therapies as well as potential new targets for therapy.

Aims - to investigate

1. Long-term prognosis and the impact of gender after cardiac resynchronization therapy (CRT)
2. If systematic screening can show whether patients with CRT and/or implantable cardioverter defibrillator (ICD) are underserved by heart transplantation (HTx) and/or left ventricular assist device (LVAD)
3. If ghrelin dysregulation in HF is due to inadequate acylation of ghrelin and whether this resolves post HTx
4. If circulating copeptin (C-terminal pro-vasopressin) is elevated and predicts prognosis in HF, and if LVAD and HTx therapy are associated with reversal of activation of the vasopressin axis
5. If levels, correlations, and prognostic impact of N-terminal pro brain natriuretic peptide (NT-proBNP), mid-regional pro atrial natriuretic peptides (MR-proANP) and mid-regional pro adrenomedullin (MR-proADM) differ by HF phenotype

ad 1 Long-term survival after cardiac resynchronization therapy

In a single centre retrospective cohort study, data on 619 patients with CRT were collected. Overall, 1-, 5- and 10-year survivals were 91%, 63% and 39%, respectively, and female gender was the only independent predictor of survival ($p=0.025$).

ad 2 Screening of patients with CRT

In a single centre screening study of 194 patients with CRT and/or ICD, 2 (1%) had confirmed indication without contraindication for HTx and 12 (6%) had confirmed indication without contraindication for LVAD.

ad 3 Acylated and unacylated ghrelin in HF and post-HTx

Acylated ghrelin was lower post HTx ($n=35$) compared to age and gender matched HF patients ($n=20$) ($p<0.001$), but des-acyl ghrelin levels were similar.

ad 4 Copeptin in HF with reduced ejection fraction (HF_{rEF}) and post HTx and LVAD

Copeptin levels were highest in patients with HF_{rEF} ($n=49$), and associated with progressive lowering post LVAD ($n=13$) and HTx ($n=22$) ($p<0.001$). Overall, copeptin correlated with markers of congestion and in patients with HF_{rEF} predicted risk of death, LVAD or HTx ($p=0.001$).

ad 5 NT-proBNP, MR-proANP and MR-proADM in HF_{rEF}, HF with preserved ejection fraction (HF_{pEF}), post HTx and LVAD

NT-proBNP and MR-proANP were higher in patients with HF_{rEF} ($n=49$), than in patients with HF_{pEF} ($n=86$) ($p<0.001$ for both), correlated with measurements of cardiac function and outcomes, whereas MR-proADM did none of the above. LVAD ($n=13$) and HTx ($n=22$) were associated with progressively decreased levels of all three biomarkers ($p<0.001$ for all biomarkers).

Conclusions

Current HF therapy improves outcomes but may be underutilized. Novel cardiovascular and/or anabolic hormones may emerge as targets for therapy. Specifically, women with CRT may have especially good prognosis; HTx and LVAD are underutilized and screening may increase the number of patients who may benefit from these treatments; ghrelin and arginine vasopressin may be involved in the pathophysiology of HF and emerge as potential novel targets; and the cardiovascular hormones BNP, ANP and ADM can characterize differences between and provide targets for potential therapy in different HF phenotypes.