Conclusion: Improvement of hemodynamic conditions in patients with continuous-flow VAD treatment leads to an alteration of shear forces, which might contribute to capillary density rarefaction.

Chronic Heart Failure - Diagnostic Methods

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Klotho is induced in human cardiomyopathy independently of circulating klotho levels

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Introduction: Klotho is an antiaging protein which exerts cardioprotection. In the kidney, trans-membrane Klotho acts as essential co-receptor of fibroblast growth factor 23 (FGF23) which has been linked to the cardiac remodeling, advent and progression of chronic heart failure (CHF). In the heart, soluble Klotho (sKlotho) protects from stress induced hypertrophy and systolic dysfunction independently of FGF23. Since the role of sKlotho in CHF is barely understood, we aimed to analyze the association of FGF23 and sKlotho upon progression of heart failure and analyzed Klotho expression in human non-ischemic cardiomyopathy (CMP).
Methods and Results: Serum levels of sKlotho and FGF23 were measured in 287 patients with CMP. Tissue samples from CMP (n = 10) and non-failing control hearts (n = 10) were analyzed for Klotho expression using 3'RACE-PCR, qRT-PCR, immunoblotting, and immunohistochemistry. In tertile-based sex-stratified analysis, individuals in the third FGF23 tertile were 4.1 times (95%CI 1.42-12.38; p = 0.009) more likely to reach an endpoint of death, heart transplantation or assist device implantation compared to first tertile. No relationship was found between sKlotho and the combined endpoint (hazard ratio 0.76 [0.45-1.2]; p = 0.299). Instead, Klotho mRNA encoding the full-length form was upregulated in human DCM hearts. Immunoblotting and immunohistochemistry confirmed upregulation of sKlotho associated with increased expression of proteases involved in cleavage of Klotho like ADAM10, ADAM17, and BACE1 in DCM hearts suggesting local cleavage of Klotho in the heart.
Conclusions: Our data indicate that in contrast to FGF23, serum sKlotho is not associated with disease severity or progression in CHF. Instead, Klotho is expressed and upregulated in diseased hearts, suggesting local cardioprotective paracrine effects.

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Neprilysin (CD10) expression on peripheral leukocytes in chronic heart failure patients

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Background: Neprilysin inhibition (NEPi) has been shown to reduce hospitalization and all-cause mortality in patients with heart failure and reduced ejection fraction (HFrEF). Since then circulating NEP concentration (sNEP) has been discussed controversially as a biomarker. Neprilysin (CD10) is known to be present on the surface of monocytes and lymphocytes as well as at higher levels on neutrophils in healthy subjects and implicated in the inflammatory response. The possible impact of NEP expression on peripheral leukocytes on sNEP levels and prognostic measures in HFrEF have not been investigated yet.
Methods: We prospectively enrolled 99 consecutive patients with stable HFrEF, who were clinically followed-up routinely. Laboratory markers including NT-proBNP were assessed. sNEP and NEP (CD10) expression on peripheral blood cells were measured by FACS analysis for all patients. The association between NEP expression and laboratory parameters as well as with sNEP levels were determined.
Results: Figure1 shows characteristic FACS expression results for patients with HFrEF with high and low expression intensities of CD10. NEP was markedly expressed on granulocytes with 94.8% (IQR 90.5-97.4) and measureable on B-cells and monocytes with 8.5% (IQR 5.3-13.5) and 0.8% (IQR 0.4-1.5) of CD10+ cells of the respective leukocyte subtype. NEP expression on T-cells was not detectable. The mean fluorescence intensity (MFI) of CD10 was 5461 (IQR 4028-6904) for granulocytes, 640 (IQR 535-740) for B-cells and 1589 (IQR 1395-1975) for monocytes. An inverse correlation of NT-proBNP could be proven with the MFI of CD10+granulocytes (r=-0.46, p < 0.001) but not with the MFI of CD10+B-cells (r=-0.13, p = 0.191) or CD10+monocytes (r = 0.07, p = 0.477). Figure2 depicts differences in MFI for CD10+granulocytes according to tertiles of selected variables, i.e. NT-proBNP, albumin, hemoglobin and butyryl-cholinesterase. sNEP concentrations were 2425pg/ml (IQR 1559-3349). sNEP concentrations correlated positively with the expression of CD10 on granulocytes (r = 0.22, p = 0.030) and with the MFI of CD10+granulocytes (r = 0.306, p = 0.003).
Conclusions: CD10 expression levels on neutrophils might reflect a distinct systemic inflammatory disposition, with low expression levels accompanying a more severe disease state reflected by NT-proBNP. Granulocyte CD10 expression correlates to measurable sNEP levels.

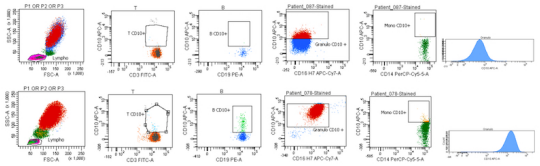

Figure 1

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Circulating Neprilysin is not a prognostic biomarker for cancer patients

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Background: The circulating form of the membrane-bound zink-metalloendopeptidase neprilysin (cNEP) as a biomarker in heart failure has been discussed controversially in recent studies. However, evidence emerges that NEP is not only implicated in the homeostasis of vasoactive peptides, but also plays a key role in tumor biology. NEP could therefor represent another link between the heart and cancer which might be of special interest in the field of cardiooncology. Concentrations of cNEP have not yet been assessed in cancer patients.
Aim: The aim of the study was to determine cNEP levels in an unselected cohort of treatment-naïve cancer patients and to investigate the association of cNEP levels with biomarkers of the heart, other organ systems and inflammatory state as well as the effect of cNEP on prognosis.
Methods: 555 consecutive patients with primary diagnosis of cancer without prior anticancer therapy were enrolled prospectively. NEP levels were determined in venous plasma samples alongside routine laboratory parameters, a set of cardiac biomarkers, i.e. N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitive TroponinT (hsTnT), mid-regional pro-atrial natriuretic peptide (MR-proANP), mid-regional pro-adrenomedullin (MR-proADM), C-terminal pro-endothelin-1 (CT-proET1) or Copeptin, and inflammatory parameters, i.e. C-reactive protein (CRP), interleukin-6 (IL-6) and serum amyloid A (SAA). All-cause mortality was defined as primary endpoint.
Results: cNEP showed a wide distribution in the total cohort with a median of 276pg/ml (IQR 0-5981), displaying a weak correlation with age [r=-0.12, p = 0.023]. cNEP showed a modest but consequent inverse rank-correlation with the inflammatory status [r=-0.14, p = 0.007 for CRP; r=-0.20, p < 0.001 for IL-6 and r=-0.18, p < 0.001 for SAA], however seemed not to be related to the functional parameters of other organ systems as the heart [r=-0.05, p = 0.367 for NT-proBNP; r=-0.10, p = 0.075 for hsTnT; r=-0.03, r=-0.02, p = 0.664 for MR-proANP; r=-0.05, p = 0.387 for MR-proADM; r = 0.07, p = 0.168 for CT-proET1 and r=-0.01, p = 0.864 for Copeptin], kidney or liver. cNEP was not associated with overall survival in the total cohort [adj.HR for ln(cNEP) 1.00, 95%CI:0.94-1.06, p = 0.887], and neither in the subgoups of solid tumors nor myeloproliferative disease, but in myelodysplatic malignancies [adj.HR for ln(cNEP) 1.27, 95%CI:1.01-1.61, p = 0.044]. Figure 1 shows the Kaplan-Meier analysis according to cNEP tertiles.
Conclusions: cNEP shows a wide distribution in human plasma of cancer patients. cNEP levels are comparable between different tumor entities and stages and lack association with outcome but for myelodysplastic disease. Moreover, no association could be revealed between cNEP and other organ system, especially the heart, assessed by a set of established cardiac biomarkers.