Elevation of circulating dipeptidyl peptidase (cDPP3) is associated with worse outcome in chronic heart failure with reduced ejection fraction

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Background. Dipeptidyl dipeptidase (DPP3) is a protease involved in the degradation of cardiovascular mediators. Increased levels of circulating DPP3 (cDPP3) have been shown to be associated with impaired myocardial contraction whereas inhibition may restore cardiac function in preclinical models. Elevated DPP3 is similarly associated with therapy refractoriness in cardiogenic shock. In contrast, data on cDPP3 levels in stable heart failure with reduced ejection fraction (HFrEF) are lacking.

Purpose. The present study aims to evaluate the impact of cDPP3 in patients with chronic HFrEF.

Methods. Consecutive patients with stable chronic HFrEF and optimal medical therapy have been enrolled prospectively from the outpatient unit of heart failure at the Medical University of Vienna between February 2016 and December 2017. Routine laboratory parameters including NT-proBNP and additionally other heart failure biomarkers as active plasma renin concentration (ARC), norepinephrine (NE), GDF-15 and copeptin have been measured by specific immunoassays. Bio adrenomedullin and DPP3 have been determined by the sphingotest® assay. All-cause mortality and heart failure hospitalization was assessed as the combined primary outcome.

Results. A total of 365 patients were included into the study. Samples were hemolytic in 40 cases, so that cDPP3 measurements were analyzed for a total of 325 patients. Median cDPP3 was 11.36ng/ml (IQR: 8.87-14.48) and cDPP3 levels were comparable for ischemic and non-ischemic etiology of HF and also for different RAS-inhibitors (Figure 1). DPP3 showed a modest correlation with NT-proBNP (r_S=0.13, p=0.024), GDF-15 (r_S=0.20, p<0.001), NE (r_S=0.27, p<0.001), copeptin (r_S=0.16, p=0.004) and bio-ADM (r_S=0.14, p=0.014) as shown in Figure 2. Increasing DPP3 was associated with worse outcome by spline analysis, whereas the driver of the primary endpoint was all-cause mortality. cDDP3 was significantly associated with all-cause mortality in univariate Cox regression [crude HR 1.15 (95% CI: 1.03-1.28), p=0.011 for an increase of 5ng/ml cDPP3] and the association remained as a trend after adjustment for NT-proBNP [adj. HR 1.12 (95% CI: 1.00-1.25), p=0.058], suggesting an independent additional value of cDPP3 to the probably most potent prognostic biomarker of HFrEF.

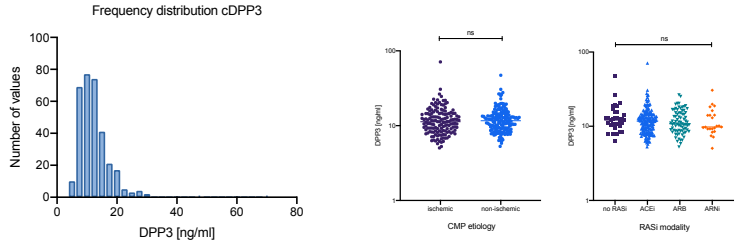
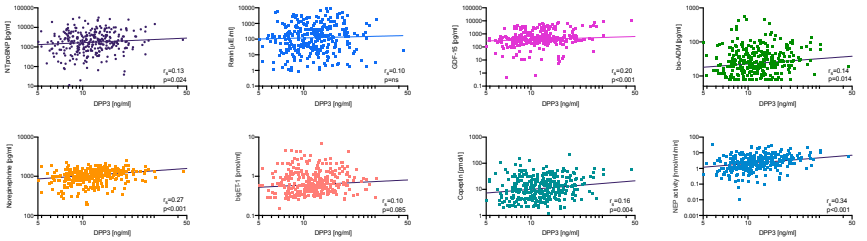


Figure 1. Neurohumoral memory in end stage heart failure patients undergoing heart transplantation or LVAD implantation. A. Individual values and median and inter-quartile ranges of NT-proBNP and plasma active renin concentration are displayed for patients undergoing HTx and LVAD implantation before and approximately 6 months after the procedure. Variables were compared by the Wilcoxon-test. ULN marks the upper limit of normal. B. Complete plasma RAS-fingerprints: numbers in brackets indicate the specific angiotensin peptides; side of spheres and numbers beside represent absolute concentrations of angiotensins (pmol/l, median value) analyzed by mass spectrometry.



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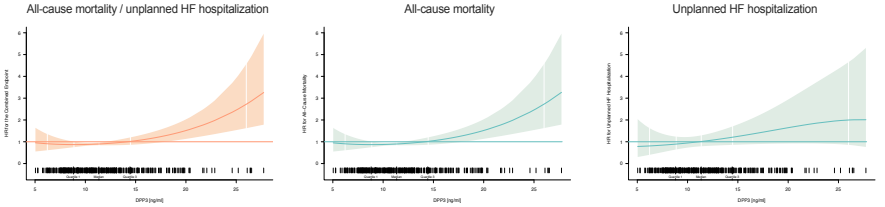

Figure 2. Neurohumoral memory in end stage heart failure patients undergoing LVAD implantation or heart transplantation. Numbers in brackets indicate the specific angiotensin peptides. Side of spheres and numbers beside represent absolute concentrations of angiotensins (pmol/l, median value) analyzed by mass spectrometry.

Conclusions. cDPP3 levels in stable HFrEF are lower compared to patients with sepsis or cardiogenic shock. cDPP3 shows a modest correlation with other heart failure biomarkers and is a risk factor for worse outcome in stable HFrEF as shown for other more critical conditions. In chronic heart failure mortality seems to increase beyond the treshhold of 15ng/ml of cDDP3 suggesting that cDPP3 could be a biomarker for advanced heart failure, a most vulnerable population which is difficult to define. The source of cDPP3 in stable HFrEF as well as its cardiodepressive potential or potentially related pathophysiological mechanisms have to be investigated in further studies.

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