# Imaging and Circulating Biomarkers – A United Approach for Secondary Tricuspid Regurgitation

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Background: Secondary tricuspid regurgitation (sTR) is frequent among patients with heart failure with reduced ejection fraction (HFrEF), however inheres considerable diagnostic challenges. The assessment of circulating biomarkers reflecting neurohumoral activation may constitute a valuable supplement to the currently imaging-based diagnostic process. This study therefore sought to investigate (i) the expression of a set of complementary biomarkers in sTR, (ii) to evaluate their association with sTR severity, and (iii) to analyse whether the combination of neurohormone measurement and echocardiographic grading improves the individual patient risk assessment.

Methods: We included 576 HFrEF patients under guideline-directed therapy recording functional, echocardiographic, invasive hemodynamic and biochemical measurements, i.e. N-terminal pro-B-type natriuretic peptide, mid-regional pro-atrial natriuretic peptide (MR-proANP), mid-regional pro-adrenomedullin, C-terminal pro-endothelin-1 (CT-pro-ET1) and copeptin.
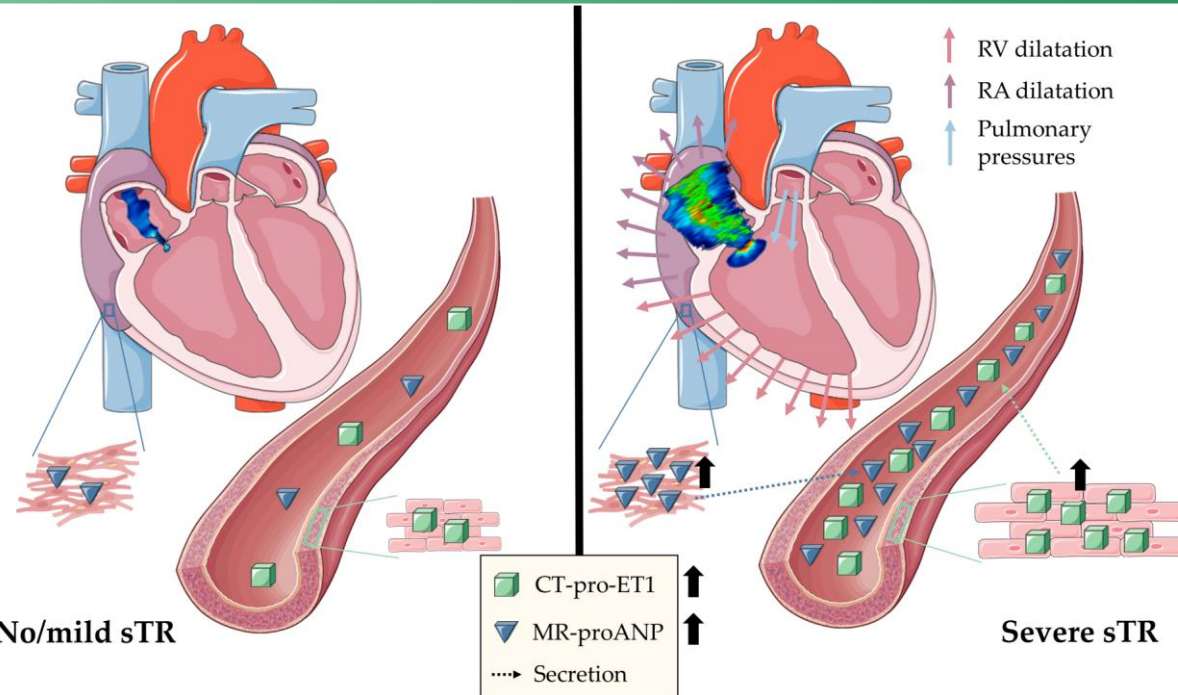
Results: Plasma levels of aforementioned neurohormones were significantly rising with increasing sTR severity (for all P<0.001). Among all measured biomarkers, CT-pro-ET1 and MR-proANP were closest related to severe sTR, even after multivariate adjustment for established clinical confounders (adj. OR 1.46; 95%CI 1.11-1.91, P=0.006 and adj. OR 1.45, 95%CI 1.13-1.87, P=0.004, respectively). By means of individual outcome in patients with moderate to severe sTR, adding the selected biomarkers (i.e. CT-pro-ET1 and MR-proANP) resulted in a substantial improvement in the discriminatory power regarding long-term mortality (C-statistic: 0.54 vs. 0.65, P<0.001; continuous NRI 57%, P<0.001).

Conclusions: Circulating biomarkers closely relate to sTR severity and correlate with hemodynamic and morphologic mechanisms of sTR. Specifically, MR-proANP and CT-pro-ET1 are closely related to the presence of severe sTR and a combined assessment with the guideline recommended echocardiographic grading leads to a significant improvement of individual risk stratification.
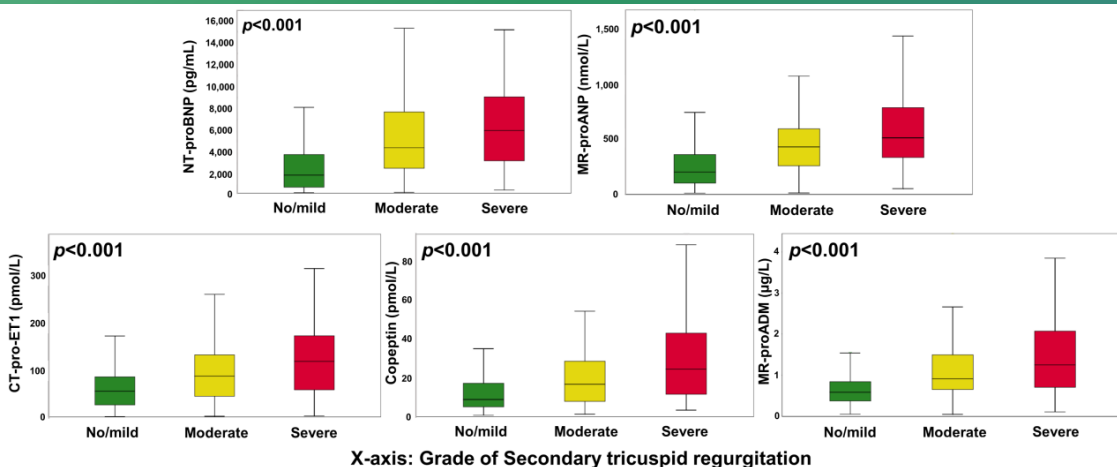

↑ RV dilatation
↑ RA dilatation
↑ Pulmonary pressures

CT-pro-ET1 ↑
MR-proANP ↑
⋯▸ Secretion

No/mild sTR

Severe sTR

Figure 1. Neurohumoral profiles in HFrEF patients with no/mild, moderate or severe tricuspid regurgitation. Levels are displayed as Tukey boxplots.

X-axis: Grade of Secondary tricuspid regurgitation

Figure 2. Correlogram investigating the correlation between neurohumoral activation and invasively measured hemodynamic parameters in HFrEF patients with secondary tricuspid regurgitation. Coloured fields indicate statistical significance, blue colour indicates direct correlation, red colour indicates indirect correlation, the shade of the colour indicates the correlation coefficient calculated by Pearson-r and referenced in the adjacent scale.