MicroRNA Assessment in Secondary Mitral Regurgitation – Evidence for Remodelling Mechanisms at a Cellular Level

MEDIZINISCHE UNIVERSITÄT WIEN

[1]Georg Spinka, [1]Philipp E. Bartko, [1]Noemi Pavo, [1] Claudia Freitag, [1] Katrin Zlabinger, [1]Suriya Prausmüller, [1]Henrike Arfsten, [1]Gregor Heitzinger, [1] Julia Mascherbauer, [1]Christian Hengstenberg, [1] Mariann Gyöngyösi, [1]Martin Hülsmann, [1]Georg Goliasch

[1]Department of Internal Medicine II, Medical University of Vienna, Austria

@ValveDisease

Background: Secondary mitral regurgitation (sMR) is associated with adverse outcome in patients with heart failure with reduced ejection fraction (HFrEF), possibly driven through malignant cardiac remodelling. MicroRNAs (miRNA/miR), small non-coding RNAs involved in post-transcriptional gene regulation, have recently been associated with the development of fibrosis and hypertrophy. This study therefore sought to assess the differences in miRNA-profiles in patients with severe sMR compared to matched disease controls, the correlation of circulating miRNAs with sMR severity as well as the prognostic implications of miRNA-levels in patients with HFrEF and severe sMR.

Methods: Sixty-six patients with HFrEF were included in this pilot study. Forty-four patients with severe sMR were matched to disease controls with no/mild sMR in a 2:1 ratio. A comprehensive panel of miRNAs (miR-21, miR-29a, miR-122, miR-132, miR-133a, and miR-let7i) was measured using real time polymerase chain reaction and related to echocardiographic assessment of sMR severity.

Results: The profiles of miR-21, miR-29a, miR-132, miR-133a, and miR-let7i differed significantly between patients with severe sMR and HFrEF controls (for all P<0.05). Moreover, we observed significant correlations between circulating miR-133a (r=-0.41, P=0.001), miR-29a (r=-0.32, P=0.009), and miR-let7i (r=-0.28, P=0.022) and sMR vena contracta width. Elevated levels of miR-133a conveyed an increased risk for cardiovascular death and/or heart failure hospitalisations with and adjusted HR of 1.85 (95% CI 1.24-2.76, P=0.003). Furthermore, Kaplan-Meier-Analysis revealed a significantly higher risk for the above-mentioned outcome in patients with severe sMR and miR-133a-levels above the median.

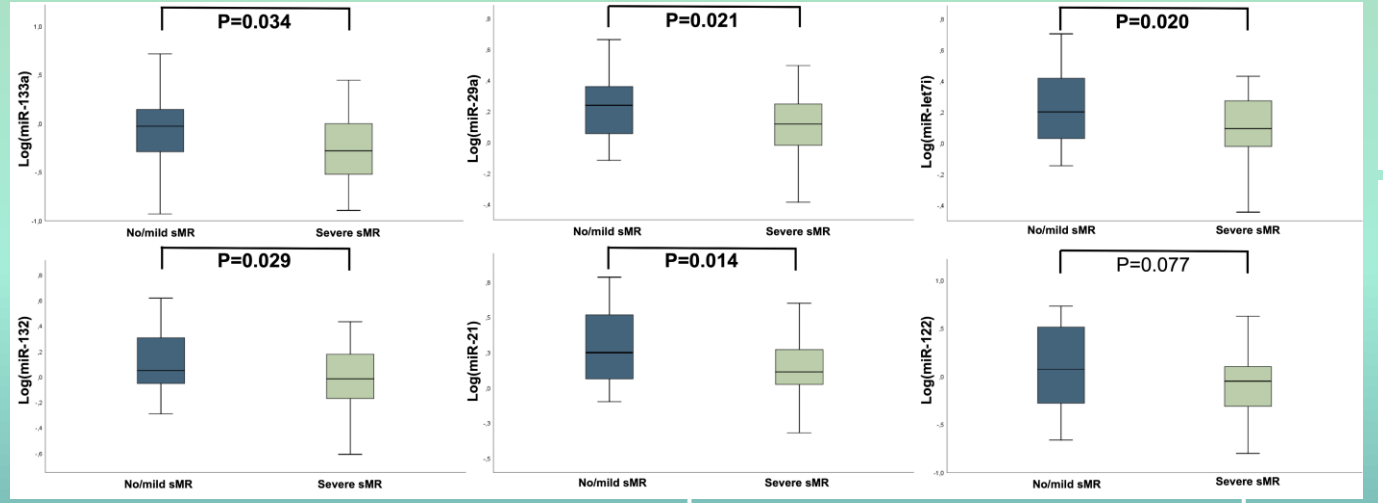

Figure 1. miRNA profiles in HFrEF patients with either severe sMR or no/mild sMR (matched controls).

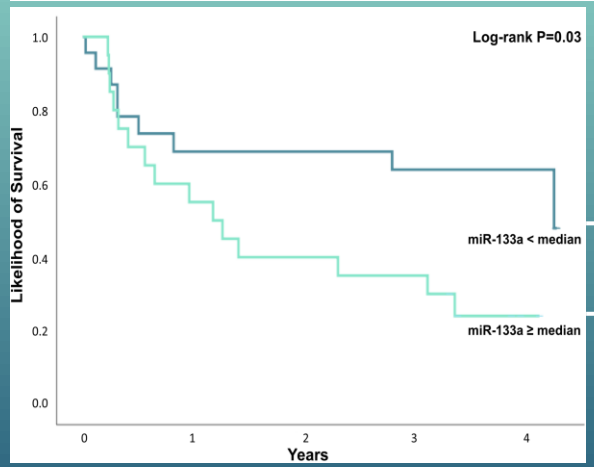

Figure 3. Kaplan-Meier estimates of the primary outcome comparing patients with severe sMR and miR-133a-levels below the median to patients with severe sMR and miR-133a-levels above the median (log-rank P=0.03).

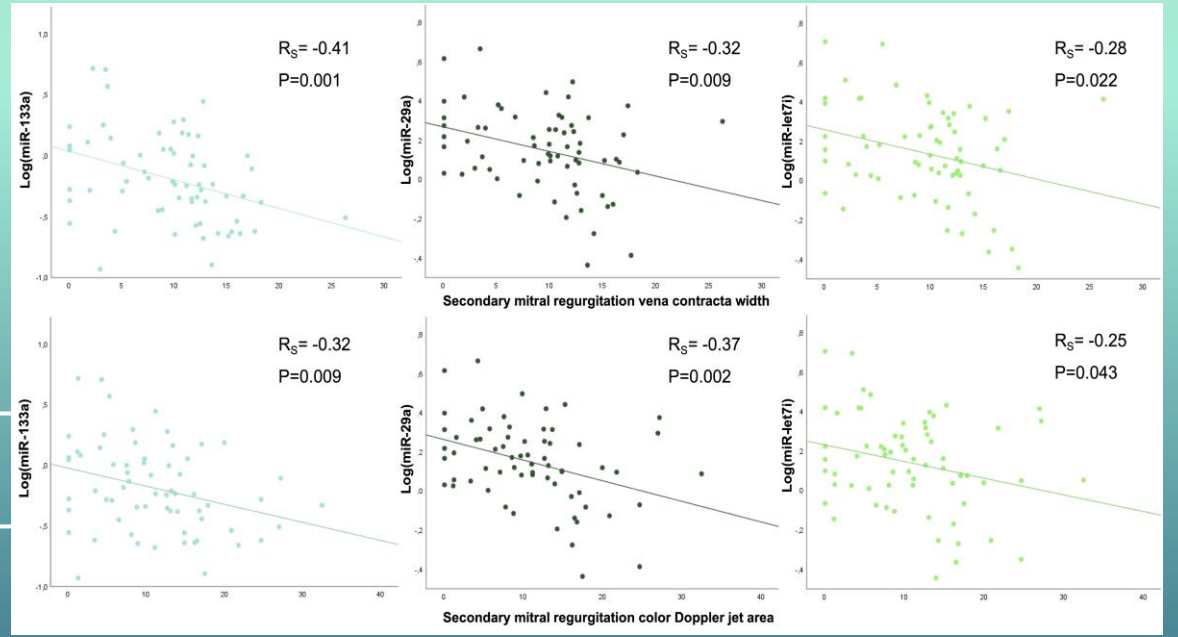

Figure 2. Scatter plot displaying the association between quantified surrogates of sMR (i.e. sMR vena contracta width and sMR regurgitant jet area) and microRNA-levels in patients with HFrEF and severe sMR or no/mild sMR (matched controls).

Conclusions: This study unveils distinct pathophysiologic mechanisms at a cellular level in patients with severe sMR compared to patients with no/mild sMR. We observed significant differences in miRNA-profiles and strong correlations of miRNAs with surrogates of sMR severity, supporting the concept that sMR drives adverse cardiac remodelling in heart failure. Finally, elevated levels of miR-133a convey an increased risk for morbidity and mortality in patients with HFrEF and severe sMR, potentially implying advanced myocardial damage.