Abstract: P3699
Circulating pro-apoptotic microRNA-122 correlates with left ventricular function (LVEF) improvement after transcatheter aortic valve replacement and influence cardiomyocyte function via microvesicle

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Background

Transcatheter aortic valve replacement (TAVR) is an established treatment option for high and intermediate risk patients with severe symptomatic aortic stenosis (AS). Whereas the majority of patients develop a left ventricular ejection fraction (LVEF) improvement after TAVR in response to TAVR-associated afterload reduction, around 50 % of patients with reduced LVEF fail to develop LVEF improvement after TAVR. MicroRNAs (miRs) are novel biomarkers and effectors of myocardial (dys)function. We aimed to explore whether circulating miRs are differently regulated in response to TAVR in patients with or without postprocedural LV-function improvement.

Methods and results

96 patients who underwent TAVR were screened for inclusion into the study. Patients with impaired LVEF (<45%) were divided into three groups according to post-procedural LVEF development assessed 6 months after TAVR by transthoracic echocardiography: No LVEF improvement, LVEF-improvement of 0-15% and >15%. Plasma samples were obtained at 3 different time points: On the day before TAVR-procedure and at days 1 and 7 post-TAVR. Taqman miR array was performed in patients without LVEF improvement group and >15% LVEF improvement. The results showed that miR-122, miR-26a, miR-192, miR-483-5p, miR-720, miR-885-5p and miR-1274 were differently expressed when compared between day 1 and day 7. Based on literature, we also quantified four miRs related to LV function and fibrosis in our collective (miR-21, miR-145, miR-199, miR-30b). We validated these 14 circulating miRs levels and found that miR-122 level significantly increased at day 7 after TAVR in the no LVEF-improvement group. The increase of miR-122 negatively correlated with LVEF improvement at both day 7 (r=−0.237 and p=0.031) and 3 months (r=−0.323 and p=0.02) after TAVR. Within the 2-year follow-up, patients with lower level of miR-122 displayed a significantly reduced cardiovascular mortality (p=0.049). Next, vesicle degradation experiment and ultracentrifugation showed that miR-122 were mainly incorporated in microvesicles (MVs). In vitro, H202 increased miR-122 level in endothelial cells and endothelial-derived MV. Gain and Loss function experiments indicated elevated miR-122 level impaired migration and proliferation on HUVECs. Cardiomyocytes incubated with MVs miR122-upregulated showed higher miR-122 expression than exosome miR122-upregulated or vesicle-free supernatant. Confocal microscopy confirmed the fluorescence-labeled EVs were absorbed by cardiomyocyte. Absorbed MVs miR122-upregulated induced apoptosis of recipient cardiomyocytes.

Conclusion

Changes of circulating pro-apoptotic miR-122 levels significantly correlate with LVEF improvement after TAVR in low LVEF patients and might be suitable to predict the long term prognosis after TAVR in this set of patients. Microvesicles can mediate the transfer of miR-122 from endothelial cells to cardiomyocytes and further influence cardiomyocyte function.
Circulating pro-apoptotic microRNA-122 correlates with left ventricular function (LVEF) improvement in patients after transcatheter aortic valve replacement and is transferred into cardiomyocytes via microvesicle.