The pathophysiologic relevance of B lymphocyte autoimmunity in patients with mitral valve disease and secondary pulmonary hypertension

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Pulmonary hypertension (PH), a common complication of left heart disease (LHD), negatively impacts on LHD patients´ morbidity and mortality. PH-LHD represents the most common type of PH and is diagnosed as mean pulmonary arterial pressure (mPAP) > 25 mmHg and a mean pulmonary arterial wedge pressure > 15 mmHg. Recent research has stressed the importance of dysregulated immunity in the pathophysiology of PH generally and changes in the B-cell homeostasis in animal models of PH-LHD specifically. Due to an inflammatory condition, autoreactive B-cells can escape central and peripheral tolerance mechanisms and, therefore, conduce to the pathogenesis of autoimmune disease which may present a so far unrecognized pathomechanism in PH-LHD. As such, deeper insight into the contribution of B-cell immunity to PH-LHD may provide for a better understanding of underlying pathophysiological processes and thus, for the identification of novel cellular therapeutic targets. Here, we hypothesized that changes in B-cell homeostasis and autoreactivity modulate disease development and severity in PH-LHD.

To this end, we analyzed whole blood samples of patients with mitral valve replacement/repair with and without PH, according to echocardiographic risk assessment. The echocardiographic assessment of PH was based on the 2015 ESC/ERS guidelines for the diagnosis and treatment of PH taking e.g., tricuspid regurgitation velocity (TRV) and early diastolic pulmonary regurgitation (PR) velocity into account and allowing for classification of patients into groups of low, intermediate or high probability of PH.

No differences could be detected in concentrations of peripheral naive B-cells (CD19+, CD27-, IgD+), total plasmablasts and plasma cells (CD19+, CD27+,CD38+), as well as total non-switched memory B-cells (CD19+, CD27+, CD38-, IgD+) and total switched memory B-cells (CD19+, CD27+, CD38+, IgD-) that were quantified in the blood of patients with mitral valve disease, correlated with the total number of B-cells (CD19+, CD3-, CD14-, CD16-, CD56-) and compared to a group of age and sex matched healthy controls. In line with these findings, immunoglobulin isotyping analyses revealed no significant differences between the patient cohort and healthy controls. Yet importantly, 75% of patients with a high probability of PH carried IgG and IgA anti-nuclear or anti-cytoplasmatic autoantibodies in their plasma, compared to 0% of healthy controls and 15,4% of patients with low probability. These results point to a potential relevance of autoantibodies as a crucial element in the pathophysiology and as prognostic marker of PH-LHD.