

BRUNO BUCHHOLZ

Autoimmunity in Heart Failure: Role of Antiadrenergic Autoantibodies

Cao N, Chen H, Bai Y, Yang X, Xu W, Hao W, Zhou Y, Chai J, Wu Y, Wang Z, Yin X, Wang L, Wang W, Liu H, Fu MLX. β 2-adrenergic receptor autoantibodies alleviated myocardial damage induced by β 1-adrenergic receptor autoantibodies in heart failure. **Cardiovasc Res.** 2018 Sep 1;114:1487-98. <http://doi.org/gdh-hft>

In physiological conditions, β 1-adrenergic receptors play a very important role in the regulation of different indicators of cardiovascular function, as heart rate and myocardial contractility. Conversely, β 2 receptors fulfill minor and less manifest functions. In pathological conditions, the role of β 1-adrenergic receptors is significantly modified and alters normal myocardial functioning, leading to damage and the poor outcome of the patient. Autoimmunity is one of the physiopathological mechanisms studied in heart failure, characterized by the production of circulating autoantibodies which react with β 1 and β 2 receptors. Anti- β 1 antibodies generate a sustained chronic activation of these receptors, leading to heart failure through cardiac dysfunction and the cellular damage it entails.

In situations in which there is great catecholamine release, as in heart failure, the activation of β 2 receptors is more important and it has been shown that they are able to counteract the hyperactivity of β 1 receptors through the inhibitory effect of the intracellular Gi protein. Same as with β 1 receptors, high levels of circulating anti- β 2 receptor autoantibodies have been detected in heart failure. However, their function is unknown in this pathology.

In this work, Cao et al. study the effect of anti- β 1 and anti- β 2 autoantibodies on heart failure structure and function and whether β 2 activation is able to inhibit overstimulated β 1 function by specific anti- β 1 autoantibodies.

The study population consisted of patients with heart failure due to coronary artery disease and dilated cardiomyopathy, with an increase of both antibodies

compared with healthy controls. The imbalance in the β 1/ β 2 autoantibody ratio is associated with cardiac dysfunction and plays a relevant role in the physiopathology of this clinical condition. This was confirmed both by in vivo experimental studies in rats with hearts failure induced by doxorubicin or isoproterenol administration, and in in vitro studies using isolated myocytes from neonatal rats. Similarly to patients, rats with heart failure showed increased levels of anti- β 1 and anti- β 2 autoantibodies, with a profile tending to an imbalance in the relationship between both proteins which was correlated with the magnitude of ventricular function damage. Interestingly, the administration of serum anti- β 1 autoantibodies (obtained from the aforementioned patients) to isolated rat myocytes increased their rate of contraction, a phenomenon only counteracted by β 2 stimulation. In addition, stimulation with anti- β 1 autoantibodies reduced isolated myocyte survival, increasing necrosis and apoptosis. These deleterious phenomena significantly decreased when anti- β 2 autoantibodies were jointly administered. These results were also verified in in vivo studies.

Rats receiving doxorubicin and with anti- β 1 autoantibody blockade had better cardiac functional and structural evolution. Conversely, blockade of anti- β 2 autoantibodies was associated with worsening heart failure and impairment.

Overall, the data obtained from the patients studied by these authors and then correlated with results from isolated myocyte and rat studies demonstrate that the increase and imbalance in the β 1 and β 2 autoantibody interrelationship plays an important role in heart failure myocardial function deterioration. Another relevant finding of this work is that anti- β 2 autoantibodies antagonize anti- β 1 autoantibodies, enabling myocardial protection by reducing cell death and improving cardiac function. Future studies to confirm these findings could contribute to assess whether the relationship between the two autoantibodies can be used as a clinical assessment factor of functional deterioration in patients with heart failure, and eventually offer new therapeutic opportunities.