Ranolazine attenuates adverse myocardial remodeling, lung capillaries and endothelial dysfunction in a model of heart failure with preserved ejection fraction

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BACKGROUND:

Approximately half of the patients with symptoms and signs of heart failure present with preserved ejection fraction (HFpEF). The prevalence of HFpEF continues to increase in the developed world (1). HFpEF is characterized by ventricular diastolic and systolic reserve abnormalities, chronotropic incompetence, stiffening of ventricular tissue, atrial dysfunction, pulmonary hypertension, impaired vasodilation and endothelial dysfunction. Systolic and diastolic dysfunction lead to increased left atrial pressure, lung capillary injury and resistance to gas transfer (2). Moreover, in HFpEF, stimuli other than pressure may trigger capillaries and small arteries remodeling, as a consequence of endothelial dysfunction, proliferation of myofibroblasts, fibrosis and extracellular matrix deposition. In parallel, loss of alveolar gas diffusion properties due to the increased path from air to blood (thickening of extracellular matrix) and deregulation of molecular mechanism involved in fluid reabsorption and clearance are observed. Changes in gas transfer not only reflect the underlying lung tissue damage but may play a role in the pathogenesis of HFpEF. Based on this knowledge and following a need to investigate new strategies, the attention, among other targets, has been directed to ranolazine (RAN). RAN by selectively inhibiting late sodium current (INa) can decrease Na+-dependent calcium accumulation and is expected to promote Ca2+ extrusion through the Na+/Ca2+ exchanger (NCX) improving myocyte relaxation and diastolic tension (3). Since hypertension is a strong risk factor, affecting up to 90 percent of HFpEF patients, in this work we investigated the effects of chronic administration of RAN on an experimental model of hypertension-triggered HFpEF.

METHODS:

Seven-weeks old Dahl salt-sensitive rats were fed a high salt diet for 5 weeks to induce hypertension. Afterwards, rats continued with a high salt diet and were administered either with vehicle or RAN (20mg/kg/die, ip) for the following 8 weeks. Hemodynamic parameters were assessed invasively. Protein expression was determined by western blot to highlight the key molecular pathways responsible for proliferation, fibrosis and extracellular matrix deposition. Masson's trichrome staining was used to detect tissue fibrosis.

RESULTS:

While systolic parameters were not altered, diastolic parameters changed in high salt animals. Hemodynamic analysis showed decreased dP/dt min, increased LVEDP, a longer time constant and a steeper slope of the end-diastolic pressure-volume relationship. Treatment with RAN attenuated these alterations and determined a reduction in mortality. Additionally, the magnitude of myocardial hypertrophy and activation of PI3K/Akt pathway associated to endothelial dysfunction

were reduced. Alterations in diastolic compliance, as a consequence of elevated myocardial stiffness, were confirmed by an increase of collagen deposition and activation of the pro-fibrotic TGF-β/SMAD3/CTGF signaling. Injury of the alveolar–capillary barrier was associated with increased levels of plasma pulmonary surfactant, which, in turn, was related to tumor necrosis factor (TNF)-α, endothelin-1 (ET1) and transforming growth factor β (TGF-β) increased levels. Extensive fibrosis observed in high salt animals, depended by the accumulation of collagen as shown by Masson's trichrome. The abundance of these proteins in the extracellular matrix is considered a major determinant of myocardial stiffness and alveolar remodeling. Moreover, the fine mechanisms for an optimal gas exchange, controlling alveolar Na+ and water metabolism were compromised in HFpEF. These effects were counteracted by RAN. Indeed, high salt rats showed a decrease in SERCA2 and an increase in NCX. Treatment with RAN reduced NCX expression and determined an increment of SERCA2 levels. Further, nitrotyrosine and oxidized dyhydroethidium levels were higher in high salt rats. RAN induced a decrement of oxidative stress, supporting the concept that reduction in ROS may mediate beneficial effects in HFpEF patients at myocardial and pulmonary levels.

CONCLUSIONS:

Our findings support the possibility that diastolic dysfunction can be attenuated by RAN indicating its ability to affect active relaxation and passive diastolic compliance. Moreover, RAN may positively modulate structural remodeling of the lung capillary network potentially ameliorating alveolar properties and gas exchange.

1. Bhatia, et al., N. Engl. J. Med. 2006;355:260–69.

2. Guazzi, et al., Prog Cardiovasc Dis. 2015;57:454-62

3. Sossalla, et al., Basic Res. Cardiol. 2011;106:263–72