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High prevalence of pharmacologically active autoantibodies in heart failure, with dual action on serotoninergic 5-HT4 and muscarinic M2 receptors
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Purpose: In adult in congestive heart failure the expression of 5-HT4 receptor is increased 4 folds. Therefore we looked for the presence of anti-S-HT4 receptor autoantibodies (AaRs) in sera of patients with heart failure.

Methods: Sera from 333 heart failure patients and 150 controls were screened against second extra cellular loop (SEC) of 5-HT4, 5-HT1, 2 adrenoceptors, AT1 and M2 muscarinic receptor, using indirect and inhibition ELISA. The ability of AaRs to decrease native corresponding receptors was explored through Fluorescent immunolabeling. AaRs’ pharmacological cells effect was explored using chronotropy on neonatal rat cardiomyocytes and H-L-I cells. Five different truncated peptides from SEC of S-HT4 were used for epitope mapping.

Results: We could confirm specific immunoreactivity only for S-HT4 and 5-HT2. We found 21 and 19 sera positive for 5-HT4 and M2 receptors respectively with 90% of exact identity for both receptors. We found the same result in control population. Peptides derived from SEL of both receptors cross-inhibit sera with S-HT4 and M2 receptors. They recognised all one and same epitope. IgG fractions patients and controls had negative chronotropic effect. The specificity of the AaRs for S-HT4 and M2 receptors were verified pharmacologically with ML10375 and atropine specific S-HT4 antagonist and M2 agonist. Clinical studies revealed that the entire positive control individuals suffered from hypertension, so the case was heart failure patients positive for the two receptors. There is a high prevalence of pharmacologically active cross-reacting AaRs against SEC of S-HT4 and M2 receptors in hypertensive heart failure patients. These AaRs may play an important role in set and pathophysiology of heart failure as they are found in hypertensive patients without yet clinical manifestation of heart disease.

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TGF-beta1 dependent acquisition of specific adhesion junctions in mitral valve prolapse
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Mitral valve prolapse (MVP) is the leading cause of mitral incompetence in Western countries. The cause of this pathology is the still unknown, although the dysregulation of TGF-beta pathway seems to play a role in familial MVP. TGF-beta may induce the expression of stress fibers (α-smooth muscle actin, SMA) in fibroblasts and the acquisition of a myofibroblastic phenotype as well as a switch of the cadherin pattern at junctional level. There are no data on molecular composition of cell-cell contact in mitral valve prolapse. Aim of this study was to evaluate whether TGF-beta pathway is activated in isolated MVP and to study the effect of this activation on differentiation of VCs in myofibroblasts and on the molecular pattern of their junctions.

Methods: Ropy mitral valves were obtained at surgery from patients (12 cases, 10 M and 2 F, mean age 53.5 ± 12.7 years) who underwent valve repair. Age and sex-matched control samples were obtained from Homograft Tissue Bank (5 cases, mean age 49 ± 9 years). Valve morphology was assessed by routinely stained histology sections. Antibodies recognizing active form of Smad2 (p-Smad2) in VCs were used. The following antibodies against junctional proteins were applied: N-cadherin, cadherin-11, VE-cadherin, α- and β-catenin, plakoglobin, protein p120. IC67 was used to assess the proliferation.

Results: MVP leaflets exhibited alterations in tissue with a fourfold increase in thickness (2.5 ± 0.8 vs 0.6 ± 0.3 mm, p < 0.0001) and increased cell density (110.0 ± 64.6 vs 51.8 ± 27.2 cells per high power field, p = 0.04) compared to the normal valves. A higher density of nuclear staining for p-Smad2 (38% vs 12%, p > 0.05) was also observed, indicating an increased activation of TGF-beta pathway.

The VCs in myomastous leaflets showed a myofibroblast differentiation (expression of α-SMA) and AJs containing high levels of cadherin-11, either exclusively or in colocalization with N-cadherin, unlike VCs from controls that were α-SMA negative and exhibited predominant expression of N-cadherin at junction level.

Conclusions: Our data support the hypothesis that an increased activation of the TGF-beta pathway may contribute to the pathogenesis of sporadic MVP, either with promotion of myofibroblastic differentiation of VCs and acquisition of a specific cadherin pattern in AJs, that confer higher resistance of cell-cell contacts in a stress environment. In its turn, myofibroblast contraction may activate latent TGF-beta from extracellular matrix. Targeting of myomastic AJs by specific anti-cadherin peptides may be used to prevent or retard mitral myocardial degeneration.

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Comparison of myocardial structural and molecular changes in rat models of type 1 and type 2 diabetes mellitus
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Cardiovascular complications are one of the main causes of mortality in diabetes mellitus (DM). There is obvious evidence demonstrating that DM leads to structural and functional changes at the level of the myocardium. In this study, we investigated and compared myocardial structural and molecular changes in rat models of type-1 and type-2 DM.

Type-1 DM was induced in Sprague-Dawley rats by single injection of streptozotocin (60mg/kg, i.p.). Continuous glucose monitoring experiments were performed 8 wk after the confirmation of diabetes. For type-2 DM, Zucker-diabetic fatty (ZDF) and ZDF-lean rats were used and experiments were performed at the age of 30–32 wk. Heart samples were stained with hematoxylin-eosin and immunohistochemical analysis was performed for nitrotyrosine, TUNEL, (terminal deoxynucleotidyl transferase dUTP nick end labeling) was used for detection of DNA-strand breaks. Different gene expression analysis was performed by quantitative real-time polymerase chain reaction.

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