

**THESIS TITLE: BASES GENÓMICAS Y CELULARES DE LA CONTRACCIÓN VENTRICULAR. PAPEL DEL RETÍCULO ENDOPLÁSMICO Y LOS CANALES IÓNICOS EN LA INSUFICIENCIA CARDÍACA HUMANA**

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**ABSTRACT:**

Heart failure is a multifactorial syndrome characterized by alterations in ventricular function and cardiac chambers dilation, being a cause of increase of morbidity, mortality and health costs. Dilated and ischemic cardiomyopathies are frequent causes of this syndrome. Despite the progress in treatment of heart failure, the prognosis has not improved significantly in the last years, because of that, we need a development of novel treatment strategies, given the limited efficacy of current therapies.

This syndrome can be associated to alterations in heart contraction. Endoplasmic reticulum is the major intracellular calcium storage necessary for heart contraction onset. On the other hand, ion channels regulate heart contraction and are responsible for the ion currents that determine and influence the action potential of heart muscle.

In this Thesis we aimed to study, in a group of patients with heart failure, the changes existing in the structural and stress response proteins of the endoplasmic reticulum, as well as the gene expression of cardiac ion channels, relating these alterations with ventricular dysfunction of these patients.

Our results showed the presence of alterations in the majority of structural and stress proteins of the endoplasmic reticulum, being the structural protein RRBP1 related to ventricular dysfunction and also to the stress protein XBP1. This evidences a specific dependency between stress and structure in this organelle and an influence of structural changes in ventricular function of patients.

Additionally, we showed different expression changes of a large number of cardiac ion channels through microarrays and RNA sequencing techniques. Of these channels, down-regulation of *CACNG8* related to ventricular function improvement and increased levels of *KCNJ2* and *KCNN3* with ventricular dysfunction in dilated cardiomyopathy. In ischemic cardiomyopathy, reduced levels of *TRPM7* channel were related to a better ventricular function. Differential gene expression of this category in both cardiomyopathies, could explain the changes in the different ion currents that affect the myocardial contraction process in heart failure.

In conclusion, we show alterations in the expression of two key components of cardiac muscle contraction that could provide novel basis for their study and regulation as possible therapeutic targets for the improvement of cardiac contractility in patients with heart failure.