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The Alzheimer's Heart: A mindful view of HFpEF

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Short summary:

Alzheimer's disease (AD) and Heart Failure (HF) are both major global health problems and have been singled-out as emerging epidemics worldwide. One in nine people older than 65 years of age has AD, and AD is the fifth cause of death in patients age 65 and older.

Our recent discovery that those conditions can coexist in the same person is an alarming prospective given that people are living longer. The prevalence of dementia in HF is computed between 30% and 80% of patients and it has been reported an estimate of HF in patients with AD in a third of the cases accounting for over 20 million people affected worldwide.

Documented hallmark of AD is the deposit of misfolded proteins in the brain forming amyloid aggregates in the neuronal tissue. We described the presence of protein aggregates in the myocardium of patients affected by DCM and HF and in the heart of patients suffering from AD. Importantly the aggregates are biochemically akin to the brain ones and the same molecular diversity of the brain deposits is

recapitulated in the myocardium of patients with primary diagnosis of cardiomyopathy or AD.

Clinically, we found that the form of HF prevalent in AD patients is of heart failure with preserved ejection fraction (HFpEF). HFpEF is a relatively new medical entity affecting nearly equal numbers of patients than the one affected by HF with reduced Ejection Fraction (HFrEF) and due to various etiologies. Being a phenotype typical of aging it is not surprising that HFpEF represents the main phenotype of Alzheimer's Cardiomyopathy.

Biosketch:

My major focus is in basic and translational research exploring the pathophysiology of heart failure from the molecule *in-silico*, to *in-vitro* and *in-vivo* animal models as well as human studies both at the cellular/tissue levels and trough clinical studies. Specifically, the fundamental direction of my laboratory is to understand the cellular and molecular mechanism that cause the onset of myocardial dysfunction and the progression to heart failure as well as genetic and environmental modifiers. Further goals are to identify biomarkers to identify patients at risk and/or to predict disease progression as well as engineer novel meaningful therapies for those patients.

Towards this goal my laboratory has evolved through innovative unexplored territories. While initially studying the molecular mechanisms of ß-adrenergic signaling, contractile and Ca^{2+} dysfunction in animal models and human cardiomyocytes, as I started my program as PI, my laboratory developed a new direction and made breakthrough discoveries that changed the paradigm for idiopathic dilated cardiomyopathy (iDCM) and heart failure. We discovered the presence of misfolded protein aggregates in the myocardium of patients with iDCM in HF placing this disease in the category of proteinopathies. The proteinopathy is accompanied with ER stress and abnormal unfolding protein response. We discovered that not only there are amyloid plaque-like and tangle-like in the heart of patients with iDCM and HF, but that they are composed of the same proteins as the aggregates in the brain of patients with Alzheimer's disease prompting the provocative term of "Alzheimer's disease of the heart". The most recent work led to the discovery that aggregates are also present in the heart of patients with AD and both hallmarks of AD pathology are present in the heart of cardiomyopathy or AD patients. Not surprisingly the failing phenotype

observed in proteinopathies is the Heart Failure with Preserved Ejection Fraction (HFpEF). HFpEF is the prevalent phenotype associated with aging and aging increases the incidence of HFpEF making HFpEF the phenotype of age-related diseases and diseases of anticipated aging such as Alzheimer Cardiomyopathy.

Most recent studies delve into 1) the mechanisms for the onset of sporadic AD heart and brain and the understanding of the effect of the gene/environment modifiers on the pathophysiology of sporadic proteinopathies; 2) the mechanisms of transmission of disease; 3) Novel mechanisms for the pathogenesis of Alzheimer's Cardiomyopathy

Relevant publications:

1. Gianni D**, Li A, Tesco G, McKay K M, Moore J, Raygor K, Rota M, Gwathmey JK, Dec GW, AretzT, Leri A, Semigran MJ, Anversa P, MacgillivrayTE, Tanzi RE, del Monte F. Protein Aggregates and Novel Presenilin Gene Variants in Idiopathic Dilated Cardiomyopathy. Circulation 2010 Mar 1. 121(10): 1216-26. doi: 10.1161/CIRCULATIONAHA.109.879510. PMCID: PMC2844798

2. Subramanian K, Gianni D, Balla C, Egidy Assenza G, Joshi M, Semigran MJ, Macgillivray TE, Van Eyk JE, Agnetti G, Paolocci N, Bamburg JR, Agrawal PB, del Monte F. Cofilin-2 Phosphorylation and Sequestration In Myocardial Aggregates: Novel Pathogenetic Mechanisms For Idiopathic Dilated Cardiomyopathy. JACC 2015; 65 (12):1199-214. doi: 10.1016/j.jacc.2015.01.031. PMCID: PMC4379451

3. Pignataro M, Di Rocco G, Lancellotti L, Bernini F, Subramanian K, Castellini E, Bortolotti CA, Malferrari D, Moro D, Valdrè G, Borsari M, del Monte F. Phosphorylated cofilin-2 is more prone to oxidative modifications on Cys39 and favors amyloid fibril formation. Redox Biology 2020; 30 101691.doi:10.1016/j.redox.2020.101691 PMID: 32863228

4. Troncone L*, Luciani M*, Coggins M, Ho CY, Smith N, Crain B, Frosh MP, del Monte F. Amyloid Ab pathology in Alzheimer's Disease Hearts. A systemic disease or protein metastatsis? JACC 2016; 68:2395-407 (* co-authorship) doi10.1016/j.jacc.2016.08.073 PMCID: PMC5142757

5. Luciani M, Montalbano M, Troncone L, Bacchin C, Uchida K, Daniele G, Jacobs Wolf B, Butler HM, Kiel J, Berto S, Gensemer C, Moore K, Morningstar J, Diteepeng, T, Albayram O, Abisambra, J, Norris RA, Di Salvo TG, Prosser B, Kayed R, del Monte F. Big tau aggregation disrupts microtubule tyrosination and causes myocardial diastolic dysfunction: from discovery to therapy. Eur Heart J 2023 May 1;44(17):1560-1570. doi: 10.1093/eurheartj/ehad205. PMID: 37122097