Abstract: P1243

Comparison of long-term clinical course and outcome of MYBPC3 - versus MYH7 - related hypertrophic cardiomyopathy.

Authors:
C Fumagalli¹, E Fedele¹, M Beltrami¹, M Maurizi¹, S Passantino², M Targetti¹, A Arretini¹, K Baldini¹, A Tomberli¹, F Mazzarotto¹, R Coppini³, C Ferrantini³, F Cecchi⁴, C Poggesi³, I Olivotto¹, ¹Careggi University Hospital (AOUC), Cardiomyopathies Unit - Florence - Italy, ²Meyer Children's Hospital, Cardiology Department - Florence - Italy, ³University of Florence - Florence - Italy, ⁴IRCCS Istituto Auxologico Italiano, San Luca Hospital - Milan - Italy,

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INTRODUCTION. The presence of sarcomere mutations is a powerful predictor of heart failure-related outcomes in Hypertrophic Cardiomyopathy (HCM). However, whether the prevalence of left ventricular (LV) dysfunction differs in patients with mutations in the two most prevalent HCM-associated genes (i.e. MYBPC3 and MYH7) is unclear.

PURPOSE. To ascertain lifetime trends in prevalence of LV dysfunction in HCM associated with pathogenic or likely-pathogenic MYBPC3 versus MYH7 mutations.

METHODS. Clinical and instrumental records of 402 HCM patients with MYBPC3 (N=251) or MYH7 (N=151) mutations were retrospectively reviewed. Presence of systolic dysfunction (ejection fraction [EF] <50%) and diastolic dysfunction (Grade II and III) were assessed for each patient. In vitro analysis of septal myectomy samples was performed to further compare electro-mechanic properties of MYBC3 and MYH7 patients.

RESULTS. Patients were diagnosed at a mean age of 39±17 years and 63% were men. At first evaluation MYBPC3-HCM patients were less frequently obstructive (15% vs 26% in MYH7; p=0.005) and had lower LVEF (61±11% vs 64±9%; p=0.01). Prevalence of diastolic dysfunction increased with age and was lowest in MYBPC3 patients <40 years at diagnosis (19.5% vs 35.4% in MYH7, p=0.043). At a mean follow-up (FU) of 13±11 years, patients developed comparable left atrium enlargement (MYBPC3 52±29 ml/m2 vs 41±18 at baseline, p<0.001; MYH7 54±25ml/m2 vs 45±22, p=0.003). Prevalence of diastolic dysfunction was also similar. MYBPC3 patients had lower LVEF at final evaluation (61±11% vs 64±9% in MYH7, p=0.01) with greater prevalence of overt systolic dysfunction (EF<50%, MYBPC3 vs MYH7: 15% vs 5%, OR: 2.3 95% CI: 1.2-5.8, p=0.013).

No significant differences were observed in terms of NYHA class change, atrial fibrillation, stroke, heart failure, appropriate ICD intervention or cardiovascular death. However, prevalence of NSVT was higher for MYBPC3 (39% vs 14% in MYH7, p<0.0001). At Cox multivariable analysis independent predictors of systolic dysfunction at follow-up were MYBPC3 positive status (HR 2.53 95% CI: 1.09-5.82, p=0.029) and age at initial evaluation (HR 1.03 95%CI 1.00-1.06, p=0.027).

In vitro cross-sectional evaluation of myocardial samples taken during septal myectomy at different ages showed a decline in contraction-relaxation properties after age 40 in MYBPC3 carriers, but preserved function in MYH7 patients (Figure).

CONCLUSIONS. In HCM patients, mutations in the MYBPC3 gene and early diagnosis are associated with slowly progressing systolic impairment leading to overt dysfunction in 15% compared to 5% in MYH7-HCM.
However, outcome was similar in the two subsets. These differences in lifetime myocardial performance between the two most common HCM-associated genes suggest diverse pathways of disease progression, potentially amenable to requiring different molecular approaches.