Age-associated changes in myocardial fibrosis amount and distribution quantified from nonlinear optical microscopy images

María Pérez-Zabalza, Laura García-Mendívil, Kostantinos A. Mountris, Laura Ordovás, Esther Pueyo

I3A, IIS Aragón, University of Zaragoza, Spain

Background: Age-associated cardiac remodeling involves alterations in the composition and organization of the extracellular matrix that affect heart's activity. The structural dynamics of collagen with age are poorly characterized in the human left ventricle (LV). In this work, we developed methods for automatic quantification of collagen characteristics from Second-Harmonic-Generation (SHG) microscopy images of middle-age and elderly individuals, and simulated in silico the effects on cardiac electrical propagation and proarrhythmicity.

Materials and Methods: We processed LV images of individuals in a range of ages. For each image, we extracted collagen and myocardial tissue binary masks, from which we quantified collagen amount. Also, we evaluated collagen distribution by computing the number of collagen pixels surrounded by a circle of at least 5 collagen pixels of radius. Differences in the density and organization of collagen in elderly vs middle-age individuals were evaluated. Computational human ventricular electrophysiology models were generated to characterize the effects of collagen changes on reentry vulnerability window (VW).

Results: The percentage of collagen in LV from elderly individuals was higher (median [Q1-Q3]: 6.07% [4.31%-8.19%]) than in middle-age individuals (3.26% [1.70%-5.58%]). Also, the percentage of collagen distributed in clusters was increased in elderly (21.44% [6.43%-52.05%]) as compared to middle-age individuals (11.4% [5.68%-24.08%]). In simulations, we observed an augment in VW as the percentage of fibrosis increased, but only for fibrosis distributions grouped in small clusters. When fibrosis was largely clustered, the impact of fibrosis amount on VW was negligible. These results suggest that cardiac proarrhythmicity induced by fibrosis depends not only on its content but also on its distribution.

Conclusion: Methods for automatic fibrosis evaluation from SHG images of human LV were developed and differences in the amount and distribution of fibrosis were found with age. Experimentally-based simulations of human LV electrophysiology allowed assessing the impact of fibrosis characteristics on proarrhythmicity.