Mechanistic investigations of pro-arrhythmic interplay between fibrosis, ischemia and ionic remodelling in hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is the most common inherited heart disease and a leading cause of sudden cardiac death (SCD) in the young. SCD risk stratification is limited at present because mechanisms of SCD are not fully understood, which has led to suboptimal allocation of implanted defibrillators. Myocardial ischemia and fibrosis on imaging identify a subgroup of HCM patients at higher risk of SCD, but whereas the independent prognostic value of fibrosis is well established, the independent role of ischemia requires further study. As mutual confounders on imaging, both ischemia and fibrosis likely contribute to arrhythmic substrates in HCM.

The present study aimed to investigate the electrophysiological mechanisms by which arrhythmic risk is modulated by the presence of diffuse fibrosis in regions of myocardial ischemia in HCM, which is expected to improve SCD risk stratification or improve therapies for this high-risk subgroup.

Using biophysically detailed computational models of cardiac electrophysiology, phase 1A acute myocardial ischemia was simulated in human HCM tissue affected by diffuse fibrosis. The hypothesis was that vulnerability to figure-of-eight re-entry would be increased by the slowing of retrograde propagation caused by fibrosis. Arrhythmic risk was quantified for cases with and without diffuse fibrosis.

Simulations of ischemic HCM tissue identified competing effects related to diffuse fibrosis. Because retrograde propagation during ischemia typically occurred when tissue excitability had scarcely recovered, diffuse fibrosis was sufficient to interrupt some re-entries by constraining the source-sink relationship of retrograde propagation. However, where re-entries occurred, fibrosis caused variability in re-entry exit points, which promoted interactions between the re-entrant wavefront and refractory wavetail of sinus rhythm. The findings suggest that the role of diffuse fibrosis during ischemia may be critically dependent on the fibrosis distribution, and that it does not always trivially increase arrhythmia inducibility.