Cellular determinants of arrhythmic rysk in hypertrophic cardiomyopathy

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Background: Hypertrophic cardiomyopathy (HCM) is the commonest inherited cardiac disease, with a prevalence of 1/500 in the general population. The most devastating consequence of HCM is sudden cardiac death (SCD) due to ventricular fibrillation, particularly common in children and young adults (age <30 years). The positive correlation between the extent of late gadolinium enhancement (LGE, reflecting myocardial fibrosis) and the arrhythmic risk in HCM suggests that ventricular arrhythmias are held to originate from the fibrotic regions, by a mechanism of electrical re-entry. However, recent data suggest that enhanced cellular automaticity (i.e. early- or delayed-afterdepolarizations, EADs or DADs-), rather than macro-reentry, may be clinically relevant in promoting ventricular arrhythmias in patients.

Purpose: Aiming to better understand the cellular and molecular mechanisms of arrhythmogenesis in HCM and to establish a reliable arrhythmic risk stratification in patients, we performed a translational study in HCM patients who underwent surgical myectomy, by combining a clinical follow-up study with in vitro assessments of cellular arrhythmogenicity in ventricular cardiomyocytes.

Methods: We retrospectively studied 61 HCM patients who underwent surgical interventricular-septum myectomy to relieve refractory obstruction-related symptoms. At the time of surgery, fresh ventricular tissue was collected and used to isolate single ventricular cardiomyocytes (CMs), which were used for patch-clamp measurements to assess the occurrence of EADs and DADs. Patients were followed up for a median time of 8 years and the occurrence of non-sustained ventricular tachycardia (NSVT) or life-threatening arrhythmic events (LAE) was monitored. Moreover, data from ECG and contract cardiac magnetic-resonance studies were collected.

Results: EADs occurred in CMs from 36% of patients and were associated with prolonged action potential duration. DADs occurred in 24% of patients and were associated with abnormalities of CM intracellular Ca2+ handling. The occurrence of NSVT/ LAE in patients was strongly associated with the presence of DADs in cardiomyocytes but not with the presence of EADs. Patients with NSVT/LAE were more likely to show specific "pro-arrhythmic" pathological ECG-patterns. Among patients with LGE, the presence of DADs in cells behaved as a necessary pre-requisite for NSVT/LAE, as none of the patients with evidence of fibrosis who were negative for DADs had arrhythmic events.

Conclusions: The presence of pro-arrhythmic changes appears to be necessary for arrhythmia generation in HCM and seems to be related with specific alterations at ECG level, that might be used as clinical arrhythmia predictors in HCM patients. Fibrosis per se is not a major predictor of arrhythmias in HCM but may contribute to generate sustained arrhythmias in the presence of substantial cellular triggers (DADs).