Flecainide and RyR2 (p 1324)

The anti-arrhythmia drug flecainide does not block ryanodine receptors, report Bannister et al.

Patients who suffer catecholaminergic polymorphic ventricular tachycardia (CPVT) exhibit dysfunctional calcium release from cardiomyocyte sarcoplasmic reticulum (SR) during times of increased adrenaline—such as during exercise or emotional stress. β-adrenergic receptor blockers are generally prescribed to minimize cardiac excitability, but for some patients the tachycardia remains poorly controlled. The drug flecainide can be given to such patients. Exactly how flecainide works in CPVT, however, is a matter of controversy. Some researchers suggest that, in addition to its known sodium-channel-blocking ability, flecainide blocks ryanodine receptors (RyR2)—the calcium ion channels in SR. Others argue, however, that flecainide only blocks ion flow through RyR2 in a non-physiological direction: from cytoplasm into SR. To settle the issue, Bannister and colleagues studied ion flow through recombinant human RyR2 channels in phospholipid bilayers. They found that flecainide partially reduced ion flow from cytosol to SR, but did not block the reverse, physiologically-relevant flow at all. Furthermore, they confirmed their findings in cells, showing that calcium release from SR was entirely normal in rat cardiomyocytes treated with flecainide. While flecainide remains an important drug for CPVT, say the authors, it should no longer be investigated as a prototypical RyR2 blocker.

IPD Meta-Analysis of Cell Studies (p 1346)

Gyöngyösi et al conduct a meta-analysis of cell-based cardiotherapy for acute myocardial infarction and find no clinical benefits.

While Fisher and colleagues’ meta-analysis indicates cell-therapy might benefit heart failure patients, Gyöngyösi and colleagues’ meta-analysis indicates the same is not true for acute myocardial infarction patients. Rather than gathering trial results from publications, Gyöngyösi and colleagues’ employed a database containing clinical information about individual patients enrolled in cell-based trials. The database, named AC-CRUE (meta-Analysis of Cell-based Cardiac StUdiEs) was established with the goal of determining the safety and efficacy of cell therapy while also enabling the comparison of characteristics between patients who benefit from therapy and those who don’t. The data analyzed was comprised from 12 randomized trials consisting of 1,252 patients who, soon after myocardial infarction, were given an intracoronary administration of bone marrow progenitor cells or, in one trial, cardiomyocytes derived cells. The data showed cell therapy had no effect on the incidence of major adverse cardiac or cerebrovascular events, nor on left ventricular function or remodeling. The authors acknowledge that some studies were excluded from analysis due to a lack of individual patient data, but point out that using such raw data enabled greater accuracy in assessing clinical and functional endpoints and thus the generation of robust conclusions.

Meta-Analysis of Cell Therapy Trials in HF (p 1361)

A meta-analysis of cell therapy trials for heart failure suggests the treatment is promising, report Fisher et al.

More than five million Americans suffer from heart failure, and that number is steadily increasing. Heart transplants or left ventricular assist devices are among the current treatment strategies, but these have limited long-term effectiveness. Preclinical research suggests progenitor cell therapy has the potential to improve function in damaged hearts. Clinical trials, however, provide a varied picture of the cells’ efficacy. Fisher and colleagues therefore compared the results of all randomized trials of cell therapy for heart failure to-date. They reviewed data from a total of 31 trials with 1,521 participants who had received bone marrow progenitor cells, skeletal myoblasts, or other progenitor types to treat ischemic or non-ischemic cardiomyopathy. Overall, their meta-analysis revealed that treatment significantly reduced mortality and rehospitalization and significantly improved exercise capacity, left ventricular function and quality of life. Worryingly however, the studies also contained a considerable risk of performance and selection bias (because approximately half were not blinded, or the allocation of patients was not concealed) and reporting bias (because more than two thirds of the papers omitted data). The results suggest that cell therapy may be a promising treatment for heart failure, but that double-blind randomized trials are sorely needed.
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