Pharmacology of Arrhythmia

It is obvious that interest in arrhythmia treatment is turning toward new devices and ablation techniques, and it is, of course, certain that failed sinus or Tawara’s node should be replaced by appropriate electronic pacemakers and that cardiac collapse by ventricular fibrillation or potentially lethal Torsades de Pointes should be stopped by electrical external or implantable defibrillators. For implanting pacemakers, only evidence of malfunction of pacemaking and atrioventricular conduction is necessary. To install the defibrillator, the genetic preponderance of occurrence of these arrhythmias, or types of ventricular arrhythmias likely to develop into fatal or other precipitating factors should be known. Knowledge of pacemaking or precise mechanisms of generation of arrhythmias in cellular and molecular levels is no longer necessary. Also for applying the ablation technique to eliminate substrates of arrhythmia, only the proper area, automatic foci or a part or the entire reentry circuit need to be known.

But how about pharmacological treatments? Is there no room for developing new antiarrhythmic drugs? Drugs are relied on for atrial fibrillation and prevention of sudden cardiac death. For developing antiarrhythmic drugs, it has been required to know the precise mechanisms of the generation of action potentials, those of different forms of action potentials, abnormalities of normal action potential which develop into arrhythmias etc. Cardiac electrophysiology consists of complex, multifactorial phenomena simultaneously occurring with channel or receptor related events. Molecular research aims to elucidate the single function of the single molecule and how drugs act on ion channels, transporters or extracellular or intracellular receptors, but how these drugs work on arrhythmias is only known from experimental or clinical arrhythmias. We still need drugs to maintain sinus rhythm after atrial defibrillation, to stop the transition to ventricular fibrillation, and drugs to target pathophysiological alterations to prevent the occurrence of lethal arrhythmias. I have been working using various arrhythmia models to test drugs. Classical antiarrhythmic drugs acting on channels have both yin and yang effects, but are still used, and probably no new comers will emerge from these categories. However there is still a need for upstream acting drugs, cardioprotective type of antiarrhythmic drugs. We have been working experimentally using coronary occlusion/reperfusion induced ventricular fibrillation. Na/H exchange inhibitors have been proved to be effective in eliminating coronary occlusion/reperfusion injury including VF, infarct size and myocardial stunning in various animal models. Despite clear effectiveness in animals, several clinical trials using these drugs in ischemia related situations failed to demonstrate clinical effectiveness. This is shocking for pharmacologists like me who believe that animal models should work well to predict clinical usefulness. Using similar models of animal cardiac ischemia, Na/Ca exchange inhibitors and statins have also been shown to suppress VF. These upstream acting drugs which prevent cardiac tissues from deteriorating to become substrates for proarrhythmias theoretically should be beneficial, and hopefully will be examined in the clinic for their actual effectiveness while taking into consideration cost. I still believe that antiarrhythmic drugs have a place in preventing premature death due to arrhythmias and that they will bring us an age where we can benefit from a “good sudden cardiac death”.

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