Background

Cardiac electrical activation disturbances and dispersion of repolarization bear important significance for the development of life threatening arhythmias. However, they are still incompletely explored. The current project aims therefore to delineate in detail the global activation, repolarization and their disturbances. With our unique data on the global sequence and dispersion of activation and repolarization we could validate the non-invasive repolarisation parameters, which are readily available for clinical use, e.g., QT dispersion, Tpeak-Tend interval, etc.

To achieve this goal, we have in Lund developed a novel electrode catheter technique for recording monophasic action potential (MAP) under the guidance of the electroanatomic mapping system CARTO. Thus the method combines the MAP recording technique and the CARTO mapping technique and becomes an unique tool for exploring the global activation and repolarization and thereby studying cardiac arhythmias and verifying the widely adopted non-invasive methods.

Our findings preliminarily demonstrated, for the first time in the world, that (a) the cardiac repolarization normally follows the same sequence as the activation, i.e., in contrary to the conventional concept that the repolarization is opposite to the activation sequence; (b) the most important factor that governs the genesis of the T wave is not transmural repolarization gradients as shown in ventricular wedge preparations, rather is the global (apico-basal) gradients in an *in vivo* heart. These are novel, breakthrough findings and have been highly valued in the research area of cardiac repolarization, as stated in an editorial on one of our published articles. Besides, we have repeatedly verified a link between an increased dispersion of repolarization and the genesis of ventricular arhythmias and atrial fibrillation in our patients.

However, our essential findings were from pig model. An important limitation is that the Purkinje system is intramural located in pigs, in contrast to the endocardial located Purkinje system in dogs and in humans. It is thus important to verify our findings from pigs on dog model and even clarify the feature directly in patients with tachyarrhythmias.

Aims

1). Further delineate the relation between myocardial activation and repolarization sequences in dogs during bi-ventricular pacing. We are now trying to use canine model to see if our findings from swine models are still valid in canins that have endocardially distributed Purkingje system as humans. More importantly, by studying both the activation and repoalrization during simultaneous left and right ventricular pacing we will be able to delineate the sequence and dispersion of repolarization and to observe collisions of the activation fronts and maybe also the repoalrization processes in the septal area, a phenomenon that bears important clinical implications but has never been explored *in vivo*. Along the same line, we would like to creat a dog model of long QT syndrome to verify if our global mapping could characterize the repolarization abnormality in that model. In addition we would collect data from patients with ventricular arrhythmias, Brugada syndrome and long-QT syndrome to verify the repolarization disturbance in these patients.

2). Further validate the wide-spreadly adopted QT dispersion, Tpeak-Tend interval measurements using our data from MAP mapping on global repolarization dispersions in animals during bi-ventricular pacing, in models of drug induced long-QT syndrome in a later stage and in patients with arrhythmias, Brugada syndrome and long-QT syndrome. In contrast with findings from myocardial wedge preparations, our *in vivo* findings have more clinical implications, especially when our findings are different from the above mentioned experiemental findings.

3). Further study the dispersion of repolarization and its implications for the genesis of ventricular tachycardia and ventricular fibrillation and atrial fibrillation in patients. This is directly patient related since all our earlier work is aimed to establish diagnostic tools and criteria for clinical use and thereby benefit our patients.

Working plan

Our working plan is described in accordance with the above aims:

(Aims 1 and 2): A new animal study is planned to start during the autumn of 2007. As mentioned in the aims, we will then perform MAP mapping under simultaneous biventricular pacing. Clinical data collections in patients with ventricular arrythmias for ICD implantation will be finished by the end of 2007. Data analysis and the writing of 1 manuscript is scheduled to the beginning of 2008. Monophasic action potential recording in patients with long-QT syndrome had been carried out in a few patients. However due the the limited number of recording sites and numer of patients no systematic findings were obtained. Our recent findings strongly encourage us to apply our MAP-mapping method in a greater scale in the clinical setting. Part of the research activities is planned to cooperate with colleagues in Dalian, Chgina, where it is possible to perform MAP mapping in drug-induced long QT syndrome in dogs. This is scheduled to conduct in 2008.

(Aim 3): We have performed MAP mapping in a number of patients with ventricular tachycardia, ventricular fibrillation and those without ventricular arrhythmias. The patient population will reach the size for the first publication by the end of 2007 and further publication of clinical data is expected in 2008 -2009. We plan olso to continue our clinical study in patients with atrial fibrillation, e.g., to explore the dispersion of atrial repolarization in the left atrium, especially local dispersions around the pulmonary veins using the activation-recovery time messurements from unipolar electrograms in patients with and without atrial fibrillation.

The combination of the current project with PhD student training: There have been 5 PhD students graduated from our group since 2002 and one is going to graduate in May this year. A new guest researcher is going to join us by the end of 2007, with the possibility to start a PhD project afterwards.

Implications

The MAP-mapping technique that we developed for delineate the global repolarization is unique in the world. It can be used in animal experiments and also in patients. The modified-tip catheter we developed for MAP recording has been CE-marked for clinical use. Our work about cardiac repolarization and its dispersion stands in the very front and has been highly valued in our research area. Our findings

bear marked theoretic significance on T-wave genesis on the ECG and is expected to improve our understanding of the underlying mechanisms for arrhythmias, especially for ventricular fibrillation and atrial fibrillation. The final purpose of our project is aimed to contribute to the development of new therapeutic methods to benefit our patients who suffer from these arrhythmias.

Preliminary results

Our preliminary findings show, for the first time in the world, that (a) the cardiac repolarization normally folllows the same sequence as the activation, i.e., in contrary to the conventional concept that the repolarization sequence is opposite to the activation sequence and this is valid even during pacing at different sites, which is going to be presented at the annual sessions of the Heart Rhythm Society in may this year; (b) the most important factor that governs the genesis of the T wave is not transmural repolarization gradients as demonstrated in ventricular wedge preparations, rather is the global (apico-basal) gradients in a *in vivo* heart; (d) We have found a clear link between an increased dispersion of myocardial repolarization and the development of ventricular arrhythmias and atrial fibrillation in our patients; (c) We found also that the generally adopted QT dispersion is not consistent with the MAP measurements of global dispersion of repolarization, but is the Tpeak-Tend interval. Similarly we have verified that the repolarization measurement from the activation-recovery time interval agreed well with the MAP measurements.

Based on the above findings, we have since 2000 published 26 originala publications (see separate publication list), 27 abstracts and 5 review articles. Additional 6 papers have been sent off for publication.

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Selected publications

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