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Review

Developing a novel comprehensive framework for the investigation of cellular and whole heart electrophysiology in the in situ human heart: Historical perspectives, current progress and future prospects

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ABSTRACT

Understanding the mechanisms of fatal ventricular arrhythmias is of great importance. In view of the many electrophysiological differences that exist between animal species and humans, the acquisition of basic electrophysiological data in the intact human heart is essential to drive and complement experimental work in animal and in-silico models. Over the years techniques have been developed to obtain basic electrophysiological signals directly from the patients by incorporating these measurements into routine clinical procedures which access the heart such as cardiac catheterisation and cardiac surgery. Early recordings with monophasic action potentials provided valuable information including normal values for the in vivo human heart, cycle length dependent properties, the effect of ischaemia, autonomic nervous system activity, and mechano-electric interaction. Transmural recordings addressed the controversial issue of the mid myocardial "M" cell.

More recently, the technique of multielectrode mapping (256 electrodes) developed in animal models has been extended to humans, enabling mapping of activation and repolarisation on the entire left and right ventricular epicardium in patients during cardiac surgery. Studies have examined the issue of whether ventricular fibrillation was driven by a "mother" rotor with inhomogeneous and fragmented conduction as in some animal models, or by multiple wavelets as in other animal studies; results showed that both mechanisms are operative in humans. The simpler spatial organisation of human VF has important implications for treatment and prevention. To link in-vivo human electrophysiological mapping with cellular biophysics, multielectrode mapping is now being combined with myocardial biopsies. This technique enables region-specific electrophysiology changes to be related to underlying cellular biology, for example: APD alternans, which is a precursor of VF and sudden death. The mechanism is incompletely understood but related to calcium cycling and APD restitution. Multielectrode sock mapping during incremental pacing enables epicardial sites to be identified which exhibit marked APD alternans and sites where APD alternans is absent. Whole heart electrophysiology is assessed by activation repolarisation mapping and analysis is performed immediately on-site in order to guide biopsies to specific myocardial sites. Samples are analysed for ion channel expression, Ca^{2+}-handling proteins, gap junctions and extracellular matrix. This new comprehensive approach to bridge cellular and whole heart electrophysiology allowed to identify 20 significant changes in mRNA for ion channels Ca^{2+}-handling proteins, a gap junction channel, a Na^{+}–K^{+} pump subunit and receptors (particularly K_{ir} 2.1) between the positive and negative alternans sites.

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Contents

1. Introduction

Understanding the mechanisms of fatal ventricular arrhythmias is important in order to develop strategies to combat the high incidence of sudden arrhythmic cardiac death, amounting to in excess of 50,000 per year in the UK alone (John et al., 2012). Although considerable progress has been made in animal models, extrapolating from these data to humans is not straightforward due to the many electrophysiological differences that exist between animal species and humans (Coronel et al., 1997; Zicha et al., 2003; Akar et al., 2004; O'Hara and Rudy, 2012). Furthermore the cardiac pathology that usually accompanies these arrhythmias is not always possible to exactly reproduce in animal models. The acquisition of basic electrophysiological data in the intact human heart, and from the hearts of patients with cardiac pathology, is therefore essential to complement experimental work in animal and in-silico models.

Ethical considerations require that techniques and protocols designed to achieve this should be free of risk and impose minimal additional burden on patients and clinical personnel. Procedures which access the heart such as cardiac catheterisation and cardiac surgery provide the opportunity to incorporate such measurements into the routine clinical procedure. Seminal in this regard was the early discovery that an electrode opposed to myocardium by suction and referenced locally produced an action potential configuration in which the entire repolarisation course faithfully represented the repolarisation of the intracellular action potentials beneath the electrode (Hoffman et al., 1959). This led to the development of a cardiac catheter which could be introduced into the heart during routine investigative procedures and so obtain measurements of the intracellular cardiac action potential duration (APD) from humans in vivo (Olsson et al., 1971). This provided a direct link with the cellular electrophysiology laboratory and hence with experimental work and theoretical mechanisms of arrhythmogenesis.

From these single site recordings of APD, available since the Seventies, techniques have evolved to enable a wide range of basic electrophysiological measurements to be recorded. At the same time strategies have been developed to enable normal and abnormal electrophysiological processes to be investigated during routine clinical procedures. Here we review the techniques that have been developed for acquiring basic electrophysiological data directly from the human subjects' hearts. We describe the information that has been obtained and how this may impact on our insight into arrhythmogenesis. Numerous and important differences between the human and animal models are highlighted, not only with respect to basic electrophysiological properties but also with regard to arrhythmia mechanisms.

2. Early work using monophasic action potential (MAP) recordings

Monophasic action potentials (MAPs) are extracellularly recorded waveforms that, under optimal conditions, can reproduce the

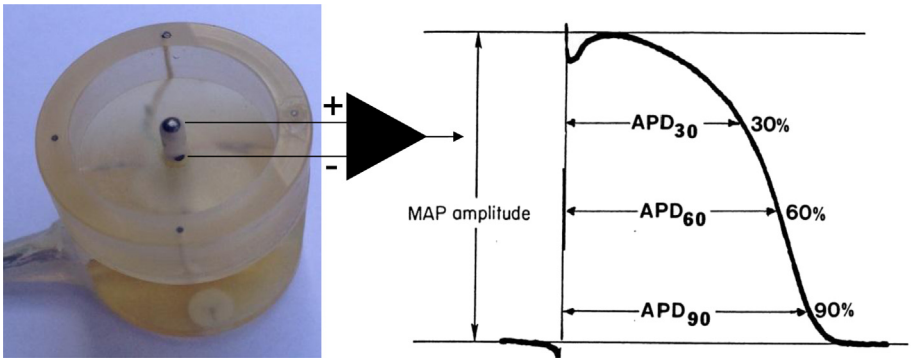

Fig. 1. Left panel: bipolar configuration of a device designed to record epicardial MAP. A suitably shaped sponge is usually incorporated in cup of holder. Right panel: A typical MAP and corresponding APD estimates. Note that the MAP amplitude is measured from baseline to the crest of the plateau. Adapted from (Franz, 1999).