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Mechano-electrical feedback in the clinical setting: Current perspectives

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ABSTRACT

Mechano-electric feedback (MEF) is an established mechanism whereby myocardial deformation causes changes in cardiac electrophysiological parameters. Extensive animal, laboratory and theoretical investigation has demonstrated that abnormal patterns of cardiac strain can induce alteration of electrical excitation and recovery through MEF, which can potentially contribute to the establishment of dangerous arrhythmias. However, the clinical relevance of MEF in patients with heart disease remains to be established.

This paper reviews upto date experimental evidence describing the response to different types of mechanical stimuli in the intact human heart with the support of new data collected during cardiac surgery. It discusses modulatory effects of MEF that may contribute to increase the vulnerability to arrhythmia and describes MEF interaction with clinical conditions where mechanically induced changes in cardiac electrophysiology are likely to be more relevant.

Finally, directions for future studies, including the need for in-vivo human data providing simultaneous assessment of the distribution of structural, functional and electrophysiological parameters at the regional level, are identified.

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1. Introduction

The electrical activity and the mechanical function of the human heart are intertwined. In normal conditions, electrical activation and repolarization ensure optimal cardiac contraction and relaxation. This electro-mechanical interaction represents the direct pathway of the mechano-electric coupling. However, this is not the only pathway of interaction. The mechano-electric feedback (MEF), a mechanism whereby mechanical deformation of the heart induces changes in the cardiac electrophysiology, has been studied for more than fifty years (Desk and Williams, 1982; Franz, 1996; Kohl et al., 1999; Kohl and Ravens, 2003; Quinn et al., 2014). However, the current understanding of MEF mechanisms derives almost entirely from animal (Calkins et al., 1991; Chen et al., 2004; Franz et al., 1992; Zabel et al., 1996a), in-vitro (Seo et al., 2010) and theoretical (Hu et al., 2013; Kuijpers et al., 2014; Quinn and Kohl, 2016) studies. These suggest that MEF may be an important factor in arrhythmogenesis and modulates cardiac risk (Quinn, 2014; Ravens, 2003). However, extrapolation to the in-vivo human heart is not straightforward because important differences exist in-vitro and in-vivo as well as between animal and human ventricular electrophysiology (O'Hara and Rudy, 2012). The precise physiological role of MEF is undetermined, but a recent animal study has suggested that MEF may also be important in the normal intact heart by synchronizing ventricular repolarization, therefore reducing tissue susceptibility to arrhythmia (Opthof et al., 2015). Extensive laboratory work has established that MEF can exacerbate arrhythmogenic substrate irritability and induce potential arrhythmic triggers, especially in the diseased heart (Franz, 1996). However, its pro-arrhythmic potential in the human heart and its precise clinical relevance is still to be determined (Babuty and Lab, 2001; Taggart, 1996; Taggart and Lab, 2008; Taggart and Sutton, 1999).

In patients, mechanical deformation of the cardiac tissue can be due to structural and functional abnormalities that cause an abnormal level of cardiac stretch, which can be acute or chronic. Cardiac stretch modulates electrophysiological dynamics by interacting with stretch-activated channels (Peyronnet et al., 2016) and calcium cycling (Calaghan et al., 2003; Calaghan and White, 1999). Non-specific cation stretch-activated channels are responsible for premature ventricular contractions, while both stretch-activated channels and calcium dynamics cause MEF-mediated changes in repolarization, and shortening and lengthening of local action potential duration (APD) depends on the precise modality and timing of cardiac stretch (Zabel et al., 1996a).

In this paper, we review recent evidence of mechanically induced changes in human cardiac electrophysiology focusing on recently published studies and using new unpublished data, we discuss clinical implications and we suggest direction for future studies.

2. Mechano-electric contribution to arrhythmia mechanisms

Soon after been first described, the potential pathological effects of MEF became of interest. It was observed that acute stretch of isolated animal hearts using left-ventricular balloons, which mimics an increase in cardiac volume, causes premature ventricular excitation, increases the propensity for arrhythmias (Stacy et al., 1992) that can transform into runs of VT if the stretch is prolonged (Hansen et al., 1990). Although the changes in ventricular loading simulated in these studies are not likely to occur in-vivo, this level of stretch may occur on a regional basis in heart disease. The most direct evidence of the existence of a MEF pathway to arrhythmia is *commotio cordis,* triggering of ventricular fibrillation by a mechanical impact to the precordial region (Kohl et al., 2001, 1999). On the other hand, precordial thump can terminate ventricular tachycardia (Barrett, 1971; Pennington et al., 1970). The link between cardiac mechanical deformation and abnormal cardiac rhythm is not limited to traumatic events. Several clinical observations suggest that long-term mechano-electric interactions may also play an important role in arrhythmogenesis. For example, ventricular wall motion abnormalities are one of the strongest clinical predictors of arrhythmic sudden death in patients with heart disease (Cicala et al., 2007), and reverse ventricular mechanical remodelling is associated with reversal of electrical remodelling and a lower rate of arrhythmia (Lellouche et al., 2011).

The establishment of dangerous ventricular arrhythmia requires a trigger, i.e. a premature beat, and a substrate (Coumel et al., 1987; Janse, 1992; Mines, 1914; Weiss et al., 2015).

Established pro-arrhythmic substrates include spatially heterogeneous repolarization (Kuo et al., 1983), temporal repolarization instabilities such as repolarization alternans (Pastore et al., 1999; Zhou et al., 2016) and short term beat-to-beat repolarization variability (Baumert et al., 2016; Thomsen et al., 2006), repolarization and conduction response to changes in heart rate (Cao et al., 1999; Ramírez et al., 2017) and disturbances in the electrical conduction such as conduction slowing (de Bakker et al., 1993; Stevenson et al., 1993) and late potentials (Breithardt et al., 1991). An interaction between refractoriness and conduction dynamics rather than a single mechanism acting in isolation determines the susceptibility to re-entry (Allessie et al., 1977; Coronel et al., 2009). In fact, re-entry requires that a wave-front of excitation finds electrically excitable tissue always ahead of it, and its likelihood depends on both conduction and repolarization dynamics. A paradigm has emerged from laboratory and theoretical studies that suggests that MEF provides a pathway to translate abnormal mechanical heterogeneity into potentially arrhythmogenic abnormal electrophysiological inhomogeneity (Kuijpers et al., 2014; Solovyova et al., 2016, 2014). Structural abnormalities such as fibrosis are relevant in this context because they can potentially provide the conditions for establishing slow conduction (through tissue uncoupling) and short repolarization (through MEF secondary to abnormal contraction), therefore increasing vulnerability to re-entry (Mines, 1914). For instance, MEF may potentially contribute to the interplay between premature activation, conduction slowing and repolarization time that is critical for the establishment of re-entrant tachycardia (Child et al., 2015; Coronel et al., 2009).

The hypothesis that MEF may favour the establishment of ventricular arrhythmia by increasing spatial inhomogeneity of repolarization, or shortening repolarization and slowing conduction at critical sites in not new (Reiter, 1996) and has been supported by

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