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Cardiac mechano-electric coupling research: Fifty years of progress and scientific innovation

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ABSTRACT

With its conceptualisation nearly fifty years ago, cardiac mechano-electric coupling (MEC) has developed from a collection of anecdotal reports into a field of research that – in spite of early scepticism – is now an accepted part of cardiac structure-function considerations. Throughout this development, MEC studies have been both driver and beneficiary of technological innovation: from sharp electrode recordings for the study of *in situ* cell responses to cell isolation and patch clamp; from early approaches to mechanical stimulation of tissue using photographic diaphragms to modern force-length feedback systems for isolated cells; and from strain gauge force recordings to genetically encodes stress probes. While much is now known about subcellular contributors to cardiac MEC, including stretch-activated ion channels and mechanical modulation of cell calcium handling, their integration at higher levels of structural complexity, and the generation of clinically-translatable knowledge, have remained challenging. This short review provides a brief summary of past achievements, current activities, and potentially rewarding future directions of cardiac MEC research. We highlight challenges and opportunities on the way to an integrated understanding of how external and intrinsic mechanical factors affect the heartbeat in health and disease, and how such understanding may improve the ways in which we prevent and/or treat cardiac pathology.

1. Whence we came

It has been almost one hundred years since Francis Arthur Bainbridge's seminal observation that right-atrial distension in anaesthetised dogs results in an acute increase in heart rate (Bainbridge, 1915), and fifty years since Klaus Deck showed a similar chronotropic response to stretch in the isolated sinoatrial node of rabbit and cat (Deck, 1964). This was followed by analogous findings from Raimund Kaufmann and Ursula Ravens (née Theophile) in isolated Purkinje fibres of rhesus monkeys (Kaufmann and Theophile, 1967), who termed these intra-cardiac, mechanically-induced electrophysiological phenomena "*Mechano-Elektrische Rückkoppelung*", or Mechano-Electric Feedback. Their work established, both conceptually and terminologically, a field of research that is now more generally referred to as cardiac mechano-electric coupling (MEC).

The past five decades have given rise to considerable progress in MEC research. Stretch-induced acceleration of early repolarisation, followed by depolarisation in later phases of the action potential (AP), and ectopic excitation of resting myocardium, were first demonstrated in frog ventricles by Max Lab in 1978 (Lab, 1978). Another ten years later, Michael R. Franz and colleagues showed that diastolic depolarization of canine ventricular tissue, caused by acute increases in intra-ventricular volume, could be used to pace the otherwise asystolic heart (Franz et al., 1989). Similar MEC responses were also reported in the atria, for example in isolated rabbit hearts by Flavia Ravelli and Maurits Allessie (Ravelli and Allessie, 1997). Direct evidence of MEC in humans was provided by Peter Taggart and colleagues, who reported an acute decrease in AP duration with increased left ventricular pressure in patients that were being weaned from cardiopulmonary bypass after surgery (Taggart et al., 1988) and by Joseph H. Levine and colleagues who showed a similar result during acute right ventricular outflow tract

Abbreviations: AP, action potential; Ca^{2+}, calcium; GsMTx-4, *Grammostola spatulata* mechanotoxin-4; MEC, mechano-electric coupling; TRPC, transient receptor potential channel.

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occlusion in patients undergoing balloon valvuloplasty for congenital pulmonary stenosis (Levine et al., 1988).

In parallel to these phenomenological reports, mechanisms underlying MEC responses were being studied at the cellular and sub-cellular level. In 1984, Falguni Guharay and Frederick Sachs reported the first single channel recordings of stretch-activated ion currents in cultured embryonic chick skeletal muscle (Guharay and Sachs, 1984). Soon after, stretch-activated currents were recorded in rat isolated ventricular myocytes (Craelius et al., 1988). The growing interest in these currents triggered efforts to clone mechano-sensitive ion channels, which was first accomplished in *Escherichia coli* (Sukharev et al., 1994), followed by structural analysis using x-ray crystallography (Chang et al., 1998).

Investigations into the role of stretch-activated currents in mechanically-induced electrophysiological changes observed at higher levels of structural and functional integration have employed various pharmacological blockers. Initially, gadolinium ions and amiloride showed promise through their ability to reduce the incidence of stretch-induced electrophysiological changes in isolated hearts (Hansen et al., 1991), atria (Bode et al., 2000), single myocytes (Kamkin et al., 2000; Zeng et al., 2000), cardiovascular smooth muscle cells (Wu and Davis, 2001), and expression systems (Hamill et al., 1992). Application of these compounds has since largely been superseded by more specific agents (for reviews, see (Caldwell et al., 1998) and (Reed et al., 2014)). For isolated cells and cultures, these include low-concentration streptomycin (Gannier et al., 1994; Nazir et al., 1995), although its ability to act *in situ* appears to be limited (Cooper and Kohl, 2005), and *Grammostola spatulata* mechanotoxin-4 (GsMTx-4) (Niggel et al., 1996), a peptide that blocks stretch-activated currents also in native cardiac tissue (Bode et al., 2001).

In view of the fact that so far no structural homologue to the bacterial mechano-sensitive ion channel has been identified in mammalian heart, a focus of recent research activities has been to determine the molecular identity of the channel(s) involved. transient receptor potential channels (TRPC) are expressed in the plasma membrane of numerous human and animal cell types, and specifically TRPC1 (Maroto et al., 2005) and TRPC6 (Sharif-Naeini et al., 2010) have been implicated in mediating cardiac MEC. In addition, a newly identified group of stretch-activated channels, 'Piezo' channels (Coste et al., 2012), is receiving significant attention, also in the cardiovascular research community. Expressed in several organs, but only weakly in bulk myocardium (Coste et al., 2010), Piezo channels display gain-of-function pathogenic mutations, which may provide a link between stretch-activated channel function and pathology (Bae et al., 2013; Demolombe et al., 2013).

At the same time, significant research efforts have been dedicated to non-sarcolemmal mediators of mechanically-induced responses, particularly stretch-effects on intracellular calcium (Ca^{2+}) handling. Stretch has been shown to acutely increase sarcoplasmic reticulum Ca^{2+} release in guinea-pig (Iribe and Kohl, 2008) and rat (Gamble et al., 1992; Iribe et al., 2009) ventricular myocytes. This appears to occur by an increase in Ca^{2+} spark rate, which may be attributable to ryanodine receptor mechano-sensitivity (Iribe et al., 2009), or local activation by mechanically-induced mitochondrial Ca^{2+} release (Belmonte and Morad, 2008). Intracellular free Ca^{2+} is also acutely affected by changes in Ca^{2+} buffering capacity *via* length-dependent modulation of the affinity of troponin-C to Ca^{2+} (Allen and Kentish, 1988). These acute mechanically-induced changes in Ca^{2+} dynamics result in a stretch-induced increase in developed tension (the classic Frank-Starling response (Cannell, 2009)) that, in the case of non-uniformly contracting myocardium, can in turn give rise to arrhythmogenic Ca^{2+} waves (ter Keurs et al., 2008). Stretch maintained over several minutes additionally increases Ca^{2+} spark rate, *via* a nitric oxide-mediated pathway (Petroff et al., 2001), and elevates intracellular Ca^{2+} with the concomitant secondary 'slow force response' (Kentish and Wrzosek, 1998; White et al., 1993).

Current understanding of integrated, organ-level MEC has been accelerated by the development of new engineering-based experimental tools. Some of the most striking examples come from tissue engineering (Brandenburger et al., 2012; Lu et al., 2013), which has demonstrated that rhythmic, phasic stretch of developing heart tissue is important for normal development and function (Zimmermann et al., 2002) and electrical activity (Hansen et al., 2010). Importantly, these experimental innovations have been complemented by the rapid advancement of computational modelling, which enables the integration of data from various spatial and temporal levels of investigation, along with the generation of novel, experimentally-testable hypotheses (Quinn and Kohl, 2013; Trayanova et al., 2011).

2. Where we are

The present volume of *Prog Biophys Mol Biol* is focussed on new technologies as drivers of cardiac biophysics research. Many of these techniques are, or will be, drivers of cardiac MEC studies as well, as evident, for instance, from another recent special issue of the journal relating to the importance of MEC in the beating heart (Kohl et al., 2012). This field is in a highly dynamic state (Kohl and Ravens, 2003), experiencing consolidation and improved integration, involving international teams with research efforts in genetics, molecular biology, biophysics, physiology, anatomy, right through to clinical application. We anticipate that this will find an illustration in the next edition of the international workshop on *Cardiac MEC and Arrhythmias*. For now, the reader is referred to a recent multi-author textbook with the same title, published in 2011 by Oxford University Press (Kohl et al., 2011).

3. To where we go

Building from a strong history and presence, the future of cardiac MEC presents exciting possibilities, benefitting from the pace of technological innovation. For instance, the introduction of transparent, hydrogel-based stretchable ionic conductors and large-strain actuators, in which electromechanical transduction is achieved without an electrochemical reaction (Keplinger et al., 2013), or transparent, light-activated bio-compatible glues (Lang et al., 2014), may allow novel approaches to non-contact electrical mapping during targeted mechanical interventions in native tissue and whole organ preparations. Also, multiplexed electronic sensor and actuator devices that are not only flexible (bending), but stretchable, may help overcome limitations of performing high-resolution electro-mechanical contact mapping *in vivo* on contracting hearts (Chung et al., 2014; Kim et al., 2012).

At the cell and tissue levels, novel methods for simultaneous mechanical manipulation and electrical measurement are being introduced. The scanning ion conductance microscope, which allows nanometre-scale non-optical mapping of surface topology and electrophysiology in living cardiac cells and tissue, can be combined with local fluid jets, so holds promise for probing unexplored sub-cellular MEC mechanisms, including their location and interaction (Lab et al., 2013). MEC research will further be enhanced by emerging non-contact methods for observation, and even intervention, as part of the burgeoning field of optogenetics. Measurements can be conducted in a cell-type specific manner, using genetically-expressed voltage- (Lundby et al., 2008; Tsutsui et al., 2010) or Ca^{2+}-sensitive (Tallini et al., 2006) fluorescent proteins. Novel means of intervention are based on genetically encoded light-sensitive ion channels, that can be used to control the activity

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