Title: 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 up-to 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.

Keyword: Mechano-electrical coupling, cardiac stretch, arrhythmia mechanisms, in-vivo human electrophysiology, cardiac mapping.

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 that 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) 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 laboratory studies (Seo et al., 2010) but its clinical relevance has yet to be demonstrated in patients.

In conclusion, MEF may facilitate arrhythmia by simultaneously inducing ectopics and promoting arrhythmogenic substrates (Quinn, 2014), especially when coupled with structural or functional abnormalities, such as fibrosis, myocardial infarction and asynchronous contraction.

In the following, we describe electrophysiological response to cardiac deformation that may results in increased vulnerability to arrhythmia.

3. Experimental evidence describing cardiac human response to different stimuli

Elegant animal and laboratory studies have demonstrated that the electrophysiological response to cardiac stretch is complex and determined by its magnitude, the velocity of the deformation, and the timing at which the stimulus is applied with respect to the action potential dynamics (Franz et al., 1992; Opthof et al., 2015; Seo et al., 2010; Zabel et al., 1996a). Experiments have shown that abrupt stretch during diastole can produce delayed afterdepolarizations (Franz et al., 1992; Seo et al., 2010), stretch applied during the early phase of repolarization causes an acceleration of the repolarization process and APD shortening, while stretch applied during the later phase of repolarization causes APD prolongation (Zabel et al., 1996a). In general, physiological ventricular loading provokes small APD shortening (H Calkins et al., 1989), whereas acute ventricular overload has been shown to increase dispersion of repolarization and induce arrhythmia in the lamb right ventricle (Chen et al., 2004), and to facilitate arrhythmia induction in the rabbit heart (Jalal et al., 1992; Reiter et al., 1997) and in a canine myocardial infarction model (H. Calkins et al., 1989).

The interaction between myocardial deformation and conduction velocity is controversial and different studies have shown mixed results (McNary et al., 2008). Some animal (Dhein et al., 2014; Quintanilla et al., 2015; Sung et al., 2003; Zabel et al., 1996b) and computational

(Kuijpers et al., 2007) studies have shown that myocardial deformation modifies conduction dynamics, while other have reported no change (Zhu et al., 1997). The underlying mechanisms of conduction dynamic changes secondary to myocardial deformation are not completely understood (Mills et al., 2008). No interaction between myocardial stretch and conduction velocity has been reported in the in-vivo human ventricle, while recent human studies have shown that atrial stretch slows atrial conduction (Coronel et al., 2010; Ravelli et al., 2011; Walters et al., 2014).

3.1 Transient modification in cardiac stretch

Electrophysiological changes secondary to abrupt modification in ventricular loading have been investigated during cardiac surgery by means of LV epicardial monophasic action potential recordings during transient aortic occlusion (Taggart et al., 1992b). Immediately after the occlusion, changes in the ventricular filling caused a significant reduction in the APD. A correlation between the reduction in the APD and the increase in the LV pressure was found. At the time of the study, the spatial organization of the electrophysiological response, which is important for the establishment of pro-arrhythmic substrate, could not be assessed due to the lack of instrumentation allowing simultaneous multi-site mapping. We recently repeated this experiment in a patient undergoing aortic valve replacement, monitoring electrophysiological changes during ventricular pacing with an epicardial multi-electrode sock containing 256 electrodes that ensures high-density mapping over both left and right ventricles (Orini et al., 2016; Taggart et al., 2014). Consistently with previous findings (Taggart et al., 1992b), Fig. 1 shows that activation recovery interval (ARI), a surrogate for APD (Coronel et al., 2006), decreased during two consecutive transient aortic clamps, while pre-clamp ARI values were restored immediately after clamp release. The smaller ARI decrease during the second clamp may be due to a smaller increase in LV loading, as suggested by the arterial pressure recordings (panel A). Spatial inhomogeneity in the ARI changes was observed, with a more pronounced decrease in the antero-lateral LV wall (panel B).

In the intact human heart, ventricular arrhythmia was previously reported during RV outflow track occlusion (Levine et al., 1988). Figure 2 describes a pattern where a LV paced beat is followed by a ventricular premature beat three times on a row during aortic clamp in a patient undergoing cardiac surgery. The unipolar electrogram recorded at each epicardial breakthrough (sites P_1, P_2 and P_3) is shown in panel A. These recordings show that the premature beats were consistent with afterdepolarization initiating after local repolarization of the previous paced beat, i.e. after the end of the T-wave of the local unipolar electrogram. Panel B shows the activation map of each paced (top row) and premature (bottom row) beats. The breakthrough of the first premature beat (B2) was in the inferior-basal LV. Interestingly, the breakthrough of the second (B4) and third (B6) premature beats corresponded to sites that

during the previous paced beat activated late (activation time > 81 ms). These premature beats may have been induced by enhanced myocardial strain at late-activated regions during LV pacing (Prinzen et al., 1999). This hypothesis should be investigated in future studies incorporating strain analysis, which provides a quantification of cardiac function as relative change in the dimension of a cardiac segment within a certain direction during a heartbeat (Lang et al., 2015). It is worth noting that a similar pattern consisting of a sequence of a weak premature beat without afterdepolarisation (as beats B2, B4 and B6) and a potentiated post-extrasystolic beat with afterdepolarisation and subsequent premature depolarisation (as beats B1, B3 and B5) was previously described in a seminal paper on MEF in the canine in-situ heart during aortic clamp (Franz, 1996; Franz et al., 1989). Furthermore, the pro-arrhythmic effect of stretch-induced premature beats secondary to post-extrasystolic potentiation has been demonstrated in elegant studies during acute ischemia (Coronel et al., 2002). Post-extrasystolic potentiation may be the underlying mechanism of the self-sustained arrhythmia shown in Fig. 2. However, this remains speculative since LV pressure was not measured.

The effect of slower (30-60 sec) modification in the ventricular filling was studied during the discontinuation of cardiopulmonary bypass, during which the heart is converted from being almost empty (on-bypass) to being filled and stretched (off-bypass) (Taggart et al., 1988). The analysis of epicardial monophasic action potential recordings revealed a correlation between arterial systolic pressure increase and local APD decrease, suggesting that myocardial stretch accelerates repolarization. Figure 3 shows results from a recent experiment where epicardial ARI were measured using a multi-electrode sock during establishment and discontinuation of cardiopulmonary bypass in a patient undergoing cardiac surgery. Consistently with previous results (Taggart et al., 1988), ARI decreased with ventricular loading.

The Valsalva manoeuvre provides a model to study the effect of rapid (about 20 sec) changes in the ventricular loading in conscious patients. The manoeuvre consists in expiring against a closed airways, which increases intrathoracic pressure, decreases venous return and reduces cardiac dimension. Hemodynamic changes elicit by this manoeuvre have been shown to terminate ventricular tachycardia (Lee and Sutton, 1982) and modify atrial flutter cycle length even after autonomic blockade (Waxman et al., 1991), demonstrating that stretch induces electrophysiological changes independently of autonomic modulation. The involvement of a non-neural mechanism was further supported by a study where supraventricular tachycardia was terminated by Valsalva manoeuvre in a transplant patient (Ambrosi et al., 1995). In a study during cardiac catheterization, the Valsalva manoeuvre was shown to induce changes in LV APD whose direction (lengthening or shortening) depended on the presence of wall-motion abnormality and/or myocardial infarction (Taggart et al., 1992a). The study population included a transplanted patient and patients taking beta-blockers to exclude confounding

effects from the autonomic nervous system. The importance of normal as opposed to abnormal wall motion in determining the electrophysiological response to changes in loading conditions in the intact human heart was confirmed in another study conducted during cardiac catheterization (James et al., 2002), where ventricular volume was modified by switching from atrio-ventricular pacing (normal ventricular filling) to ventriculo-atrial pacing (reduced ventricular filling). An increase in repolarization heterogeneity (measured as QT dispersion, which is now considered an imprecise estimator of repolarization dispersion) was observed in patients with abnormal ventricular function and not in patient with normal ventricular function (James et al., 2002).

Recently, human investigations have been conducted to assess MEF-mediated changes in the human atrium. A study performed in patients undergoing cardiac surgery has shown that atrial stretch imposed by rapid volume expansion decreased conduction velocity and introduced signal fractionation in the right superior PV–LA junction (Walters et al., 2014). While a study conducted during electro-anatomical mapping where atrial loading was modified by atrioventricular pacing, has reported a decrease in conduction velocity and an increase in vulnerability to atrial fibrillation after acute atrial stretch (Ravelli et al., 2011).

3.2 Sustained stretch

Acute reduction in LV pressure following balloon valvuloplasty and angioplasty has been shown to reduce dispersion of ventricular repolarization (Sarubbi et al., 2004). In this study, surface-ECG markers of repolarization dispersion were calculated 24 h before and after surgery in patients affected by severe congenital aortic stenosis and patients with severe coarctation of aorta. These results were consistent with previous investigation where surface ECG markers (QTc) showed a prolongation of repolarization after unloading of the right ventricle due to valvuloplasty (Levine et al., 1988). In this study, confirmation of the surface ECG findings were obtained using RV monophasic action potential recordings, which showed prolongation of repolarization after valvuloplasy and shortening of repolarization during RV outflow tract occlusion. These studies did not use cardiac pacing to eliminate possible confounding effect of heart rate changes due to cardiac stretch (Kohl et al., 1999), but have used mathematical repolarization correction instead.

3.3 Cardiovascular and respiratory oscillations

Mechano-electric feedback is thought to contribute to respiratory sinus arrhythmia, the heart rate variability in synchrony with respiration. In fact, although respiratory sinus arrhythmia is mainly driven by autonomic nervous system modulation (Eckberg, 2009; Grossman and Taylor, 2007), there is evidence that stretch of the sino-atrial node due to respiratory-related changes in atrial volume introduce a respiratory oscillation in the heart rate (Kohl et al., 1999).

Furthermore, these oscillations are not abolished by complete autonomic blockade and have been reported in the transplanted heart (Bernardi et al., 1990, 1989). Similarly, a MEF mechanism has been suggested to cause respiratory oscillations in the cycle length of human atrial flutter (Masè et al., 2009) that persist after autonomic blockade (Ravelli et al., 2008). In the intact human heart, atrial flutter rate also fluctuates in synchrony with cyclic variations in atrial volume secondary to ventricular contractions (Lammers et al., 1991; Ravelli et al., 1994), further supporting an interplay between cardiovascular mechanisms and electrophysiological changes mediated by MEF.

Recent work has revealed the existence of respiratory (Hanson et al., 2012) and low-frequency (Hanson et al., 2014) oscillations in the dynamic of human ventricular repolarization that is independent of heart rate variability. Analysis of intra-cardiac recordings from patients taking autonomic blockade suggested that they may not be entirely due to autonomic mechanisms (van Duijvenboden et al., 2015). Accordingly, MEF has been shown to be able to induce low-frequency oscillations in synchrony with Mayer waves (Julien, 2006) independently of beta-adrenergic stimulation in a computational model of the human ventricular myocyte (Pueyo et al., 2016). In the computational model, MEF interacted synergistically with adrenergic stimulation to increase the amplitude of low-frequency APD oscillations, which in pathological conditions were seen to cause arrhythmia.

3.4 Chronic stretch

A prolonged change in the sequence or rate of ventricular activation is known to produce long-term changes in the electrophysiology. During ventricular pacing, a normal contraction pattern is modified and early-activated regions are mechanically unloaded, whereas late-activated regions undergo early systolic stretch followed by supra-normal systolic shortening (Prinzen et al., 1999).The underlying mechanisms of electrical remodelling are not clear, but animal studies have suggested that MEF has a role (Jeyaraj et al., 2007; Sosunov et al., 2008). According to this hypothesis, asynchronous activation causes abnormal ventricular strain, in particular in the late-activated regions, where the local APD is prolonged through a MEF mechanism. This establishes an increased gradient of ventricular repolarization that manifests in the modification of the T-wave of the surface ECG (Jeyaraj et al., 2007). Furthermore, an elegant study in an ex-vivo rabbit model has shown that ventricular loading, pressure and contractility are all requirements to induce repolarization modification after change in the activation sequence, while electrical remodelling may be induced by stretching the ventricular wall without changing the activation sequence (Sosunov et al., 2008).

Cardiac resynchronization therapy (CRT) provides an interesting model to study the contribution of MEF to electrical remodelling in patients. Local LV APD decreases in heart

failure patients that respond to CRT with more than 15% reduction in LV end-systolic volume after 6 months, while it increased in non-responders (Chen et al., 2013). Furthermore, a non-linear relation between changes in local LV repolarization and strain has been found, where the decrease in APD was associated with local decrease in time-to-peak radial, circumferential, and longitudinal strains (Chen et al., 2016). These results are consistent with other studies where electrophysiological changes during CRT were assessed through surface electrocardiographic analysis (Lellouche et al., 2011). Further studies are needed to better understand the interaction between activation and repolarization sequences in the intact human heart (Srinivasan et al., 2016) and the role of MEF in the process of electro-mechanical remodelling (Kirchhof et al., 2011; Veire and Bax, 2011).

4 Clinical settings

Mechano-electric feedback is thought to establish pro-arrhythmic conditions in presence of abnormal patterns of cardiac stretch, which may be promoted by structural abnormalities, including fibrosis, myocardial infarction, hypertrophy, etc. The interaction between cardiac structure, function and electrophysiology is complex and difficult to disentangle. In the following, we briefly describe clinical settings where MEF may play an important role. These can be divided in conditions of transient and chronic stretch. In the former, transient stretch can increase the arrhythmic risk, which decreases when the mechanical disturbance is removed. In the latter, sustained cardiac pressure and overload is thought to be related to a higher rate of ventricular arrhythmia.

4.1 Transient stretch

4.1.1 Commotio cordis

Commotio cordis is a syndrome that demonstrates the arrhythmogenic potential of MEF. This fatal disruption of heart rhythm is due to an impact to the chest at a critical time during ventricular repolarization. The electrical disturbance is caused by acute stretch of the myocytes, not any mechanical damage or pre-existing cardiac disease (Kohl et al., 2001). Commotio cordis is the most extreme clinical manifestation of pathological MEF in which the mechanical contribution is established. Therefore, it is likely that stretch affects cardiac electrical activity in subtler ways.

4.1.2 Mitral valve prolapse

Patients with mitral valve prolapse, stenosis or insufficiency have a high incidence of arrhythmias (Coronel et al., 2010; Lévy, 1997). The regurgitation of blood puts strain on the right atrium, increases ventricular volume load and therefore increases stretch of the myocardium. In patients that have experienced complex arrhythmias as complications, there

is often fibrosis of the papillary muscles and the LV wall, which is indicative of stretch and excessive contact of the prolapsed valve (Noseworthy and Asirvatham, 2015).
Mitral stenosis involves atrial stretch and stretch-related structural changes and is associated with conduction delay, increased dispersion of conduction, and conduction asymmetry. These changes are immediately reversible by normalization of the pressure gradient via percutaneous transvenous mitral balloon valvotomy (Coronel et al., 2010).

4.1.3 Cardiac alternans.

Repolarization alternans, a modification of the repolarization pattern occurring every other beat, is an established marker of increased arrhythmic risk (Bloomfield, 2004; Rosenbaum et al., 1994), which is mediated by calcium handling dynamics (Laurita and Rosenbaum, 2008; Zhou et al., 2016). Mechanical alternans, an alternation of strong and weak beats as measured by blood pressure, is a marker with prognostic value in heart failure (Kim et al., 2014), dilated cardiomyopathy (Hirashiki et al., 2006) and pulmonary artery hypertension (Ito et al., 2012). Since calcium plays a pivotal role in both repolarization dynamics and contraction, cardiac alternans may represent a link between mechanical dysfunction and electrical instability (Laurita and Rosenbaum, 2008). Electrical and mechanical alternans may sometimes occur simultaneously (Kodama et al., 2004; Selvaraj et al., 2011; Sutton et al., 1991), but their precise interaction is not completely understood.

An in-vivo canine study has also demonstrated that acute volume overload increased T-wave alternans and reduced the heart rate at which T-wave alternans first appeared (Narayan et al., 2007), suggesting another possible link between cardiac stretch and electrical instability.

Recently, interaction between mechanical deformation and repolarization alternans has been investigated using computational modelling (Radszuweit et al., 2015; Yapari et al., 2014). In particular, it has been suggested that myocardial deformation can suppress repolarization alternans (Yapari et al., 2014), something that we have observed during transient aortic occlusion in patients undergoing cardiac surgery. Figure 4 shows a time-series of ARI measured from an epicardial unipolar electrogram during pacing at 109 bpm that exhibits repolarization alternans before and after aortic clamp. However, during aortic clamp ARI alternans almost vanishes. If supported by further data, this observation would demonstrate a link between cardiac mechanics and repolarization alternans.

4.2 Chronic stretch

4.2.1 Dyssynchronous Heart Failure

An interaction between mechanical and electrical remodelling in heart failure is supported by several observations: 1. Approximately half of cardiac deaths in this population are due to ventricular arrhythmia, 2. impaired LV ejection fraction is at present the main criterium for ICD implantation, and 3. APD prolongation is a hallmark of heart failure.

The MADIT-CRT trial has demonstrated that in patients with LV dysfunction, reverse mechanical remodelling, i.e. a reduction in the LV end-systolic volume, was associated with a significant reduction in the risk of subsequent life-threatening ventricular arrhythmias (Barsheshet et al., 2011). Similarly, reverse LV mechanical remodelling is associated with a reduction of electrocardiographic indices of repolarization dispersion and a lower rate of arrhythmias (Lellouche et al., 2011). In CRT, lead position directed by echocardiography to the area of last contraction reduces the risk of arrhythmias (Moubarak et al., 2014), which previously arose due to mechanical dyssynchrony (Haugaa et al., 2014).

A significant and positive association between pulmonary artery diastolic pressure and arrhythmic risk has been also recently found (Reiter et al., 2013). Further evidence supporting a MEF contribution to arrhythmogenesis in heart failure is given by the association between indirect estimates of volume overload and malignant ventricular tachyarrhythmia (Ip et al., 2011) and by the association between B-Type Natriuretic Peptide, which is secreted in response to excessive stretch of the heart, and sudden cardiac death (Berger et al., 2002).

These clinical studies support mechanistic (Chen et al., 2016, 2013) and theoretical (Kuijpers et al., 2014) investigations that suggest that MEF is likely to be relevant in heart failure. Further investigation is required to elucidate these mechanisms.

4.2.2 Hypertrophy

Clinical observations find hypertrophy to be linked with an increase in arrhythmias (Wolk, 2000) whilst animal models show it can increase the risk of a stretch-induced arrhythmias specifically (Evans et al., 1994). In rat, hypertrophy increases the myocardium's sensitivity to pressure changes (especially during perfusion with low K+ to induce hypokalaemia) and produces arrhythmias that are more readily fatal (Evans et al., 1994). An increase in wall thickness would increase mechanical gradients across the ventricular wall resulting in arrhythmogenesis if stretch were nonphysiologic.

4.2.3 Coronary artery disease

Coronary artery disease is often associated with wall-motion abnormalities, which can promote inhomogeneous regional myocardial deformation and modify electrophysiological

parameters through MEF. This has been experimentally demonstrated in a study involving patients undergoing surgery for coronary artery by-pass grafting, where LV function was assessed by echocardiography and epicardial APD was measured in 9 segments using a multielectrode grid (Opthof et al., 2012). Twenty three patients were studied in 3 groups: Patients with normal wall motion, patients with one or more hypokinetic segments, patients with one or more akinetic/dyskinetic segments. Mean APD was not different among the three groups, but higher dispersion of repolarization was found in the hypokinetic and akinetic/dyskinetic group with respect to the normal group, which showed the lowest dispersion of repolarization. These differences were independent from the presence of myocardial infarction. The author suggested that wall-motion abnormality induces simultaneous APD lengthening and shortening in different cardiac regions therefore increasing spatial dispersion of repolarization (Opthof et al., 2012). Another study shows that patients with segmental wall motion abnormalities are predisposed to ventricular ectopic beats during an increase in systolic aortic pressure (Siogas et al., 1998).

In post myocardial infarction patients, ventricular loading is thought to be an important arrhythmogenic parameter as demonstrated in studies were LV afterload reduction also reduced arrhythmia events and mortality (Durrer et al., 1982; Mukherjee et al., 1976).

Several animal studies have demonstrated that electro-mechanical coupling is also important during acute ischemia (Barrabés et al., 2002; Coronel et al., 2002; Horner et al., 1994; Parker, 2004), where mechanical inhomogeneity may induce ectopics, increase dispersion of repolarization and promote arrhythmia. In particular, stretch-induced ectopics originate from the ischaemic border-zone after post-extrasystolic potentiated contractions following premature beats (Coronel et al., 2002).

However, in a recent study using a porcine model of acute ischemia, stretch-activated channels blockade did not reduce the incidence of ventricular arrhythmia with respect to control (Barrabés et al., 2015). Acute ischemia is a complex phenomenon where multiple events occur simultaneously (Orini et al., 2017) and additional important electrophysiological factors should be taken into account (Janse and Wit, 1989; Pogwizd and Corr, 1987). This includes the fact that the measurement of MEF modulation of repolarization may be altered by post-repolarization refractoriness, a mechanism that develops during acute ischemia whereby refractoriness no longer corresponds to APD (Coronel et al., 2012).

5 Open questions and Direction for future studies

The experimental and clinical studies reviewed in this paper suggest that MEF may contribute to the establishment of dangerous ventricular arrhythmias. However, the effective arrhythmic

risk associated with MEF in patients is yet to be assessed. The precise evaluation of the clinical relevance of MEF is further complicated by the fact that the effect of MEF in the in-situ heart depends on the spatial and temporal organization of mechanical deformation during contraction and relaxation, which is difficult to measure, especially in abnormal conditions. The main limitation in the assessment of the clinical relevance of MEF is the lack of human data. For obvious reasons related to the difficulty of inducing controlled cardiac stretch modifications in the clinical settings and data acquisition, few human in-vivo experiments have investigated the electrophysiological response to mechanical stimuli in patients. Future investigation should try to combine structural, functional and electrophysiological information integrating different technologies (Suzuki et al., 2016), including cardiac MRI for assessment of diffuse fibrosis and myocardial infarction (Ambale-Venkatesh and Lima, 2014; Ashikaga, 2005), echocardiography for strain analysis, including novel technology that uses very high temporal and spatial resolution for improved assessment of strain (Bunting et al., 2016), and cardiac mapping for assessment of activation and repolarization dynamics. The use of new multi-parametric epicardial socks integrating sensors for electrical and functional measurements may also be beneficial in future studies (Xu et al., 2014). CRT devices offer the possibility of assessing electro-mechanical remodelling by relating regional strain to changes in local repolarization via the leads (Chen et al., 2016, 2013), and may be used to further investigate electro-mechanical remodelling. Electro-anatomical mapping systems can provide a detailed assessment of electro-mechanical coupling during electrophysiological studies (Gyöngyösi and Dib, 2011; Kroon et al., 2015; Ravelli et al., 2011) and they may play an important role in future human studies. Finally, the study of the interaction between non-invasive electrocardiographic and echocardiographic parameters (Sauer et al., 2012) may help in the discrimination between normal and abnormal mechano-electric coupling in a wider population.

Improvement in the ability to collect new information in in-human in-vivo studies should be paralleled by the development of computational electro-mechanical models (Colli Franzone et al., 2016; Hu et al., 2013; Kuijpers et al., 2012; Niederer et al., 2006; Trayanova et al., 2011) to enable interpretation of results and generation of new hypotheses and biomarkers (Quinn and Kohl, 2013).

Many open questions deserve further investigation. A fundamental issue to be addressed is the link between abnormal load, distribution of myocardial strain and electrophysiological modification in the in-situ normal and abnormal human heart. It is known that the electrophysiological response depends on the type of mechanical stimulation, i.e. fast or slow, acute or chronic, and that it is modulated by mechanical and functional properties of the tissue, i.e. presence of fibrosis, contraction abnormality etc..Extensive ongoing research in cellular

and animal models is being conducted, but this should be complemented by human studies to determine MEF involvement in arrhythmogenesis in terms of electrophysiological temporal and spatial heterogeneity as well as arrhythmia inducibility. This should include the study of cycle length dependency of the MEF response (Horner et al., 1996; Taggart and Lab, 2008) and its interaction with repolarization and conduction velocity restitution (Orini et al., 2016). The interaction with concomitant autonomic nervous system modulation deserves further attention as it may modify and enhance the electrophysiological response (Pueyo et al., 2016).

Given its established modulatory effect, the integration of MEF mechanisms into current arrhythmia management may have enormous potential for improving antiarrhythmic strategies, which would greatly benefit from the combination of mechanical, functional and electrophysiological parameters into an integrated framework which includes MEF pathways.

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Figure legends

Figure 1: Electrophysiological changes during transient aortic occlusion measured using an epicardial multi-electrode sock during cardiac surgery. A: Activation recovery interval (ARI), a surrogate for local APD, decreased, while activation time (AT) did not change during two consecutive clamps. B: Spatial distribution of ARI changes (ΔARI) demonstrating spatial variability and more pronounced ARI reduction in the LV during the two clamps.

Figure 2: Electrophysiological parameters during aortic clamp in a patient undergoing cardiac surgery as revealed by high-density multielectrode sock epicardial mapping. A: Top panel shows unipolar electrograms measured at the epicardial breakthrough (P1, P2 and P2) of 3 premature beats (B2, B4 and B6). Bottom panel shows arterial blood pressure. B: Activation maps of 3 paced beats (B1, B3 and B5) followed by a premature beat (B2, B4 and B6). Note that epicardial breakthroughs and activation patterns of premature beat are all different (along with colour maps). Epiacardial breakthroughs are in sites of previous late activation.

Figure 3: Electrophysiological parameters during establishment and discontinuation of cardiopulmonary bypass in a patient undergoing cardiac surgery. Top: Arterial blood pressure. Bottom: Mean repolarization (RT), activation (AT) and activation recovery interval (ARI)

measured during the intervals marked by horizontal lines in the top panel. Bars and whiskers represent mean and standard error evaluated across recordings from the epicardial multi-electrode sock. Statistically significant difference ($P<0.01$, Wilcoxon sign-rank test) are shown with an asterisk.

Figure 4: An example of interaction between ventricular stretch and repolarization alternans. ARI alternans, a surrogate for APD alternans, from an epicardial unipolar electrogram before, during and after aortic clamp.

References

Allessie, M.A., Bonke, F.I.M., Schopman, F.J.G., 1977. Circus movement in rabbit atrial muscle as a mechanism of tachycardia. III. The “leading circle” concept: a new model of circus movement in cardiac tissue without the involvement of an anatomical obstacle. Circ. Res. 41, 9–18. doi:10.1161/01.RES.41.1.9

Ambale-Venkatesh, B., Lima, J. a. C., 2014. Cardiac MRI: a central prognostic tool in myocardial fibrosis. Nat. Rev. Cardiol. 12, 18–29. doi:10.1038/nrcardio.2014.159

Ambrosi, P., Habib, G., Kreitmann, B., Faugère, G., Métras, D., 1995. Valsalva manoeuvre for supraventricular tachycardia in transplanted heart recipient. Lancet 346, 713. doi:10.1016/S0140-6736(95)92331-4

Ashikaga, H., 2005. Electromechanical analysis of infarct border zone in chronic myocardial infarction. AJP Hear. Circ. Physiol. 289, H1099–H1105. doi:10.1152/ajpheart.00423.2005

Babuty, D., Lab, M.J., 2001. Mechanoelectric contributions to sudden cardiac death. Cardiovasc. Res. 50, 270–279. doi:10.1016/S0008-6363(01)00255-3

Barrabés, J.A., Garcia-Dorado, D., Padilla, F., Agulló, L., Trobo, L., Carballo, J., Soler-Soler, J., 2002. Ventricular fibrillation during acute coronary occlusion is related to the dilation of the ischemic region. Basic Res. Cardiol. 97, 445–451. doi:10.1007/s003950200051

Barrabés, J.A., Inserte, J., Agulló, L., Rodríguez-Sinovas, A., Alburquerque-Béjar, J.J., Garcia-Dorado, D., 2015. Effects of the Selective Stretch-Activated Channel Blocker GsMtx4 on Stretch-Induced Changes in Refractoriness in Isolated Rat Hearts and on Ventricular Premature Beats and Arrhythmias after Coronary Occlusion in Swine. PLoS One 10, e0125753. doi:10.1371/journal.pone.0125753

Barrett, J.S., 1971. Chest thumps and the heart beat. N. Engl. J. Med. 284, 392–393.

Barsheshet, A., Wang, P.J., Moss, A.J., Solomon, S.D., Al-Ahmad, A., McNitt, S., Foster, E., Huang, D.T., Klein, H.U., Zareba, W., Eldar, M., Goldenberg, I., 2011. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation TrialCardiac Resynchronization Therapy). J. Am. Coll. Cardiol. 57, 2416–2423. doi:10.1016/j.jacc.2010.12.041

Baumert, M., Porta, A., Vos, M.A., Malik, M., Couderc, J.P., Laguna, P., Piccirillo, G., Smith, G.L., Tereshchenko, L.G., Volders, P.G.A., 2016. QT interval variability in body surface ECG: Measurement, physiological basis, and clinical value: Position statement and

consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electroph. Europace 18, 925–944. doi:10.1093/europace/euv405

Berger, R., Huelsman, M., Strecker, K., Bojic, A., Moser, P., Stanek, B., Pacher, R., 2002. B-Type Natriuretic Peptide Predicts Sudden Death in Patients With Chronic Heart Failure. Circulation 105, 2392 LP-2397.

Bernardi, L., Keller, F., Sanders, M., Reddy, P.S., Griffith, B., Meno, F., Pinsky, M.R., 1989. Respiratory sinus arrhythmia in the denervated human heart. J. Appl. Physiol. 67, 1447–55.

Bernardi, L., Salvucci, F., Suardi, R., Soldá, P.L., Calciati, A., Perlini, S., Falcone, C., Ricciardi, L., 1990. Evidence for an intrinsic mechanism regulating heart rate variability in the transplanted and the intact heart during submaximal dynamic exercise? Cardiovasc. Res. 24, 969–981. doi:10.1093/cvrese/24.12.969

Bloomfield, D.M., 2004. Microvolt T-Wave Alternans Distinguishes Between Patients Likely and Patients Not Likely to Benefit From Implanted Cardiac Defibrillator Therapy: A Solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Conundrum. Circulation 110, 1885–1889. doi:10.1161/01.CIR.0000143160.14610.53

Breithardt, G., Cain, M.E., El-Sherif, N., Flowers, N.C., Hombach, V., Janse, M., Simson, M.B., Steinbeck, G., 1991. Standards for analysis of ventricular late potentials using high-resolution or signal-averaged electrocardiography. A statement by a Task Force Committee of the European Society of Cardiology, the American Heart Association, and the American College of Ca. Circulation 83, 1481–8. doi:10.1161/01.CIR.83.4.1481

Bunting, E., Lambrakos, L., Kemper, P., Whang, W., Garan, H., Konofagou, E., 2016. Imaging the Propagation of the Electromechanical Wave in Heart Failure Patients with Cardiac Resynchronization Therapy. Pacing Clin. Electrophysiol. 40, 35–45. doi:10.1111/pace.12964

Calaghan, S.C., Belus, A., White, E., 2003. Do stretch-induced changes in intracellular calcium modify the electrical activity of cardiac muscle? Prog. Biophys. Mol. Biol. 82, 81–95. doi:10.1016/S0079-6107(03)00007-5

Calaghan, S.C., White, E., 1999. The role of calcium in the response of cardiac muscle to stretch. Prog. Biophys. Mol. Biol. 71, 59–90. doi:10.1016/S0079-6107(98)00037-6

Calkins, H., Levine, J.H., Kass, D.A., 1991. Electrophysiological effect of varied rate and extent of acute in vivo left ventricular load increase. Cardiovasc. Res. 25, 637–644.

doi:10.1093/cvrese/25.8.637

Calkins, H., Maughan, W.L., Kass, D.A., Sagawa, K., Levine, J.H., 1989. Electrophysiological effect of volume load in isolated canine hearts. Am J Physiol 256, H1697-706.

Calkins, H., Maughan, W.L., Weisman, H.F., Sugiura, S., Sagawa, K., Levine, J.H., 1989. Effect of acute volume load on refractoriness and arrhythmia development in isolated, chronically infarcted canine hearts. Circulation 79, 687–697. doi:10.1161/01.CIR.79.3.687

Cao, J.M., Qu, Z., Kim, Y.H., Wu, T.J., Garfinkel, a, Weiss, J.N., Karagueuzian, H.S., Chen, P.S., 1999. Spatiotemporal heterogeneity in the induction of ventricular fibrillation by rapid pacing: importance of cardiac restitution properties. Circ. Res. 84, 1318–1331. doi:10.1161/01.RES.84.11.1318

Chen, R.L., Penny, D.J., Greve, G., Lab, M.J., 2004. Stretch-induced regional mechanoelectric dispersion and arrhythmia in the right ventricle of anesthetized lambs. Am. J. Physiol. Heart Circ. Physiol. 286, H1008–H1014. doi:10.1152/ajpheart.00724.2003

Chen, Z., Hanson, B., Sohal, M., Sammut, E., Child, N., Shetty, A., Boucher, R., Bostock, J., Gill, J., Carr-White, G., Rinaldi, C.A., Taggart, P., 2013. Left Ventricular Epicardial Electrograms Show Divergent Changes in Action Potential Duration in Responders and Nonresponders to Cardiac Resynchronization Therapy. Circ. Arrhythmia Electrophysiol. 6, 265–271. doi:10.1161/CIRCEP.112.000148

Chen, Z., Hanson, B., Sohal, M., Sammut, E., Jackson, T., Child, N., Claridge, S., Behar, J., Niederer, S., Gill, J., Carr-White, G., Razavi, R., Rinaldi, C.A., Taggart, P., 2016. Coupling of ventricular action potential duration and local strain patterns during reverse remodeling in responders and nonresponders to cardiac resynchronization therapy. Heart Rhythm 13, 1898–1904. doi:10.1016/j.hrthm.2016.06.014

Child, N., Bishop, M.J., Hanson, B., Coronel, R., Opthof, T., Boukens, B.J., Walton, R.D., Efimov, I.R., Bostock, J., Hill, Y., Rinaldi, C.A., Razavi, R., Gill, J., Taggart, P., 2015. An activation-repolarization time metric to predict localized regions of high susceptibility to reentry. Heart Rhythm 12, 1644–53. doi:10.1016/j.hrthm.2015.04.013

Cicala, S., de Simone, G., Roman, M.J., Best, L.G., Lee, E.T., Wang, W., Welty, T.K., Galloway, J.M., Howard, B. V., Devereux, R.B., 2007. Prevalence and Prognostic Significance of Wall-Motion Abnormalities in Adults Without Clinically Recognized Cardiovascular Disease: The Strong Heart Study. Circulation 116, 143–150.

doi:10.1161/CIRCULATIONAHA.106.652149

Colli Franzone, P., Pavarino, L.F., Scacchi, S., 2016. Joint influence of transmural heterogeneities and wall deformation on cardiac bioelectrical activity: A simulation study. Math. Biosci. 280, 71–86. doi:10.1016/j.mbs.2016.08.003

Coronel, R., de Bakker, J.M.T., Wilms-Schopman, F.J.G., Opthof, T., Linnenbank, A.C., Belterman, C.N., Janse, M.J., 2006. Monophasic action potentials and activation recovery intervals as measures of ventricular action potential duration: Experimental evidence to resolve some controversies. Heart Rhythm 3, 1043–1050. doi:10.1016/j.hrthm.2006.05.027

Coronel, R., Janse, M.J., Opthof, T., Wilde, A.A., Taggart, P., 2012. Postrepolarization refractoriness in acute ischemia and after antiarrhythmic drug administration: Action potential duration is not always an index of the refractory period. Heart Rhythm 9, 977–982. doi:10.1016/j.hrthm.2012.01.021

Coronel, R., Langerveld, J., Boersma, L.V.A., Wever, E.F.D., Bon, L., van Dessel, P.F.H.M., Linnenbank, A.C., van Gilst, W.H., Ernst, S.M.P.G., Opthof, T., van Hemel, N.M., 2010. Left atrial pressure reduction for mitral stenosis reverses left atrial direction-dependent conduction abnormalities. Cardiovasc. Res. 85, 711–718. doi:10.1093/cvr/cvp374

Coronel, R., Wilms-Schopman, F.J.G., Degroot, J.R., 2002. Origin of ischemia-induced phase 1b ventricular arrhythmias in pig hearts. J. Am. Coll. Cardiol. 39, 166–176. doi:10.1016/S0735-1097(01)01686-2

Coronel, R., Wilms-Schopman, F.J.G., Opthof, T., Janse, M.J., 2009. Dispersion of repolarization and arrhythmogenesis. Heart Rhythm 6, 537–543. doi:10.1016/j.hrthm.2009.01.013

Coumel, P., Zimmermann, M., Funck-Brentano, C., 1987. Exercise test: arrhythmogenic or antiarrhythmic? Rate-dependency vs. adrenergic-dependency of tachyarrhythmias. Eur. Heart J. 8, 7–15.

de Bakker, J.M., van Capelle, F.J., Janse, M.J., Tasseron, S., Vermeulen, J.T., de Jonge, N., Lahpor, J.R., 1993. Slow conduction in the infarcted human heart. “Zigzag” course of activation. Circulation 88, 915–926. doi:10.1161/01.CIR.88.3.915

Desk, R., Williams, L., 1982. Contraction-excitation feedback in myocardium. Physiological basis and clinical relevance MJ Lab Circ. Res. 1982;50;757-766. Circ. Res. 50, 757 LP-766.

Dhein, S., Englert, C., Riethdorf, S., Kostelka, M., Dohmen, P.M., Mohr, F.-W., 2014. Arrhythmogenic effects by local left ventricular stretch: effects of flecainide and streptomycin. Naunyn. Schmiedebergs. Arch. Pharmacol. 387, 763–775. doi:10.1007/s00210-014-0988-y

Durrer, J.D., Lie, K.I., van Capelle, F.J., Durrer, D., 1982. Effect of sodium nitroprusside on mortality in acute myocardial infarction. N. Engl. J. Med. 306, 1121–1128. doi:10.1056/NEJM198205133061901

Eckberg, D.L., 2009. Point:counterpoint: respiratory sinus arrhythmia is due to a central mechanism vs. respiratory sinus arrhythmia is due to the baroreflex mechanism. J. Appl. Physiol. 106, 1740–2; discussion 1744. doi:10.1152/japplphysiol.91107.2008

Evans, S.J., Levi, A.J., Jones, J. V, 1994. Wall stress induced arrhythmia is enhanced by low potassium and early left ventricular hypertrophy in the working rat heart. Cardiovasc. Res. 28, 555–562. doi:10.1016/S0008-6363(96)88534-8

Franz, M.R., 1996. Mechano-electrical feedback in ventricular myocardium. Cardiovasc. Res. 32, 15–24.

Franz, M.R., Burkhoff, D., Yue, D.T., Sagawa, K., 1989. Mechanically induced action potential changes and arrhythmia in isolated and in situ canine hearts. Cardiovasc. Res. 23, 213–223. doi:10.1093/cvrese/23.3.213

Franz, M.R., Cima, R., Wang, D., Profitt, D., Kurz, R., 1992. Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. Circulation 86, 968–78. doi:10.1161/01.CIR.86.3.968

Grossman, P., Taylor, E.W., 2007. Toward understanding respiratory sinus arrhythmia: Relations to cardiac vagal tone, evolution and biobehavioral functions. Biol. Psychol. 74, 263–285. doi:10.1016/j.biopsycho.2005.11.014

Gyöngyösi, M., Dib, N., 2011. Diagnostic and prognostic value of 3D NOGA mapping in ischemic heart disease. Nat. Publ. Gr. 8, 393–404. doi:10.1038/nrcardio.2011.64

Hansen, D.E., Craig, C.S., Hondeghem, L.M., 1990. Stretch-induced arrhythmias in the isolated canine ventricle. Evidence for the importance of mechanoelectrical feedback. Circulation 81, 1094–1105. doi:10.1161/01.CIR.81.3.1094

Hanson, B., Child, N., Van Duijvenboden, S., Orini, M., Chen, Z., Coronel, R., Rinaldi, C.A., Gill, J.S., Gill, J.S., Taggart, P., 2014. Oscillatory behavior of ventricular action potential duration in heart failure patients at respiratory rate and low frequency. Front. Physiol. 5,

414. doi:10.3389/fphys.2014.00414

Hanson, B., Gill, J., Western, D., Gilbey, M.P., Bostock, J., Boyett, M.R., Zhang, H., Coronel, R., Taggart, P., 2012. Cyclical modulation of human ventricular repolarization by respiration. Front. Physiol. 3 SEP, 379. doi:10.3389/fphys.2012.00379

Haugaa, K.H., Marek, J.J., Ahmed, M., Ryo, K., Adelstein, E.C., Schwartzman, D., Saba, S., Gorcsan, J., 2014. Mechanical dyssynchrony after cardiac resynchronization therapy for severely symptomatic heart failure is associated with risk for ventricular arrhythmias. J. Am. Soc. Echocardiogr. 27, 872–879. doi:10.1016/j.echo.2014.04.001

Hirashiki, A., Izawa, H., Somura, F., Obata, K., Kato, T., Nishizawa, T., Yamada, A., Asano, H., Ohshima, S., Noda, A., Iino, S., Nagata, K., Okumura, K., Murohara, T., Yokota, M., 2006. Prognostic value of pacing-induced mechanical alternans in patients with mild-to-moderate idiopathic dilated cardiomyopathy in sinus rhythm. J. Am. Coll. Cardiol. 47, 1382–1389. doi:10.1016/j.jacc.2005.10.069

Horner, S.M., Dick, D.J., Murphy, C.F., Lab, M.J., 1996. Cycle length dependence of the electrophysiological effects of increased load on the myocardium. Circulation 94, 1131–1136.

Horner, S.M., Lab, M.J., Murphy, C.F., Dick, D.J., Zhou, B., Harrison, F.G., 1994. Mechanically induced changes in action potential duration and left ventricular segment length in acute regional ischaemia in the in situ porcine heart. Cardiovasc. Res. 28, 528–34. doi:10.1093/cvrese/28.4.528

Hu, Y., Gurev, V., Constantino, J., Bayer, J.D., Trayanova, N.A., 2013. Effects of Mechano-Electric Feedback on Scroll Wave Stability in Human Ventricular Fibrillation. PLoS One 8, e60287---e60287. doi:10.1371/journal.pone.0060287

Ip, J.E., Cheung, J.W., Park, D., Hellawell, J.L., Stein, K.M., Iwai, S., Liu, C.F., Lerman, B.B., Markowitz, S.M., 2011. Temporal associations between thoracic volume overload and malignant ventricular arrhythmias: A study of intrathoracic impedance. J. Cardiovasc. Electrophysiol. 22, 293–299. doi:10.1111/j.1540-8167.2010.01924.x

Ito, M., Kodama, M., Kashimura, T., Obata, H., Mitsuma, W., Hirono, S., Tomita, M., Ohno, Y., Tanabe, N., Aizawa, Y., 2012. Comparison of patients with pulmonary arterial hypertension with versus without right-sided mechanical alternans. Am. J. Cardiol. 109, 428–431. doi:10.1016/j.amjcard.2011.09.034

Jalal, S., Williams, G.R., Mann, D.E., Reiter, M.J., 1992. Effect of acute ventricular dilatation on fibrillation thresholds in the isolated rabbit heart. Am. J. Physiol. 263, H1306-10.

James, P.R., Hardman, S.M.C., Taggart, P., 2002. Physiological changes in ventricular filling alter cardiac electrophysiology in patients with abnormal ventricular function. Heart 88, 149–52.

Janse, M.J., 1992. The premature beat. Cardiovasc. Res. 26, 89–100. doi:10.1093/cvrese/26.2.89

Janse, M.J., Wit, A.L., 1989. Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. Physiol. Rev. 69, 1049–169.

Jeyaraj, D., Wilson, L.D., Zhong, J., Flask, C., Saffitz, J.E., Deschênes, I., Yu, X., Rosenbaum, D.S., 2007. Mechanoelectrical feedback as novel mechanism of cardiac electrical remodeling. Circulation 115, 3145–3155. doi:10.1161/CIRCULATIONAHA.107.688317

Julien, C., 2006. The enigma of Mayer waves: Facts and models. Cardiovasc. Res. 70, 12–21. doi:10.1016/j.cardiores.2005.11.008

Kim, R., Cingolani, O., Wittstein, I., McLean, R., Han, L., Cheng, K., Robinson, E., Brinker, J., Schulman, S.S., Berger, R.D., Henrikson, C.A., Tereshchenko, L.G., 2014. Mechanical alternans is associated with mortality in acute hospitalized heart failure prospective mechanical alternans study (mas). Circ. Arrhythmia Electrophysiol. 7, 259–266. doi:10.1161/CIRCEP.113.000958

Kirchhof, P., Breithardt, G., Hammwöhner, M., Goette, A., 2011. Evidence for mechano-electric coupling from clinical trials on heart failure, in: Peter Kohl, Frederick Sachs, and M.R.F. (Ed.), Cardiac Mechano-Electric Coupling and Arrhythmias. Oxford University Press, Oxford, UK, pp. 402–406. doi:10.1093/med/9780199570164.003.0055

Kodama, M., Kato, K., Hirono, S., Okura, Y., Hanawa, H., Yoshida, T., Hayashi, M., Tachikawa, H., Kashimura, T., Watanabe, K., Aizawa, Y., 2004. Linkage Between Mechanical and Electrical Alternans in Patients with Chronic Heart Failure. J. Cardiovasc. Electrophysiol. 15, 295–299. doi:10.1046/j.1540-8167.2004.03016.x

Kohl, P., Hunter, P., Noble, D., 1999. Stretch-induced changes in heart rate and rhythm: clinical observations, experiments and mathematical models. Prog Biophys Mol Biol 71, 91–138. doi:10.1016/S0079-6107(98)00038-8

Kohl, P., Nesbitt, A.D., Cooper, P.J., Lei, M., 2001. Sudden cardiac death by Commotio cordis: Role of mechano-electric feedback. Cardiovasc. Res. 50, 280–289. doi:10.1016/S0008-6363(01)00194-8

Kohl, P., Ravens, U., 2003. Cardiac mechano-electric feedback: Past, present, and prospect.

Prog. Biophys. Mol. Biol. 82, 3–9. doi:10.1016/S0079-6107(03)00022-1

Kroon, W., Lumens, J., Potse, M., Suerder, D., Klersy, C., Regoli, F., Murzilli, R., Moccetti, T., Delhaas, T., Krause, R., Prinzen, F.W., Auricchio, A., 2015. In vivo electromechanical assessment of heart failure patients with prolonged QRS duration. Heart Rhythm 12, 1259–67. doi:10.1016/j.hrthm.2015.03.006

Kuijpers, N.H.L., Hermeling, E., Bovendeerd, P.H.M., Delhaas, T., Prinzen, F.W., 2012. Modeling Cardiac Electromechanics and Mechanoelectrical Coupling in Dyssynchronous and Failing Hearts. J. Cardiovasc. Transl. Res. 5, 159–169. doi:10.1007/s12265-012-9346-y

Kuijpers, N.H.L., Hermeling, E., Lumens, J., ten Eikelder, H.M.M., Delhaas, T., Prinzen, F.W., 2014. Mechano-electrical coupling as framework for understanding functional remodeling during LBBB and CRT. Am. J. Physiol. Heart Circ. Physiol. 306, H1644-59. doi:10.1152/ajpheart.00689.2013

Kuijpers, N.H.L., ten Eikelder, H.M.M., Bovendeerd, P.H.M., Verheule, S., Arts, T., Hilbers, P.A.J., 2007. Mechanoelectric feedback leads to conduction slowing and block in acutely dilated atria: a modeling study of cardiac electromechanics. AJP Hear. Circ. Physiol. 292, H2832–H2853. doi:10.1152/ajpheart.00923.2006

Kuo, C.S., Munakata, K., Reddy, C.P., Surawicz, B., 1983. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential durations. Circulation 67, 1356–1367. doi:10.1161/01.CIR.67.6.1356

Lammers, W.J.E.P., Ravelli, F., Disertori, M., Antolini, R., Furlanello, F., Allessie, M.A., 1991. Variations in human atrial flutter cycle length induced by ventricular beats: Evidence of a reentrant circuit with a partially excitable gap. J. Cardiovasc. Electrophysiol. 2, 375–387.

Lang, R.M., Badano, L.P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., Flachskampf, F.A., Foster, E., Goldstein, S.A., Kuznetsova, T., Lancellotti, P., Muraru, D., Picard, M.H., Rietzschel, E.R., Rudski, L., Spencer, K.T., Tsang, W., Voigt, J.-U., 2015. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J. Am. Soc. Echocardiogr. 28, 1–39.e14. doi:10.1016/j.echo.2014.10.003

Laurita, K.R., Rosenbaum, D.S., 2008. Cellular mechanisms of arrhythmogenic cardiac alternans. Prog. Biophys. Mol. Biol. 97, 332–347. doi:10.1016/j.pbiomolbio.2008.02.014

Lee, Y.C., Sutton, F.J., 1982. Valsalva termination of ventricular tachycardia. Circulation 65,

1287–1288. doi:10.1161/01.CIR.65.6.1287

Lellouche, N., De Diego, C., Boyle, N.G., Wiener, I., Akopyan, G., Child, J.S., Shivkumar, K., 2011. Relationship between mechanical and electrical remodelling in patients with cardiac resynchronization implanted defibrillators. Europace 13, 1180–1187. doi:10.1093/europace/eur106

Levine, J.H., Guarnieri, T., Kadish, A.H., White, R.I., Calkins, H., Kan, J.S., 1988. Changes in myocardial repolarization in patients undergoing balloon valvuloplasty for congenital pulmonary stenosis: evidence for contraction-excitation feedback in humans. Circulation 77, 70–77. doi:10.1161/01.CIR.77.1.70

Lévy, S., 1997. Factors predisposing to the development of atrial fibrillation. Pacing Clin. Electrophysiol. 20, 2670–2674. doi:10.1111/j.1540-8159.1997.tb06115.x

Masè, M., Disertori, M., Ravelli, F., 2009. Cardiorespiratory interactions in patients with atrial flutter. J. Appl. Physiol. 106, 29–39. doi:10.1152/japplphysiol.91191.2008

McNary, T.G., Sohn, K., Taccardi, B., Sachse, F.B., 2008. Experimental and computational studies of strain-conduction velocity relationships in cardiac tissue. Prog. Biophys. Mol. Biol. 97, 383–400. doi:10.1016/j.pbiomolbio.2008.02.023

Mills, R.W., Narayan, S.M., McCulloch, A.D., 2008. Mechanisms of conduction slowing during myocardial stretch by ventricular volume loading in the rabbit. Am. J. Physiol. Heart Circ. Physiol. 295, H1270–H1278. doi:10.1152/ajpheart.00350.2008

Mines, G.R., 1914. On circulating excitations in heart muscles and their possible relation to tachycardia and fibrillation. Trans. R. Soc. Canada IV, 43–52.

Moubarak, G., Ritter, P., Daubert, J.C., Cazeau, S., 2014. First experience of intraoperative echocardiography-guided optimization of cardiac resynchronization therapy delivery. Arch. Cardiovasc. Dis. 107, 169–177. doi:10.1016/j.acvd.2014.03.001

Mukherjee, D., Feldman, M.S., Helfant, R.H., 1976. Nitroprusside Therapy. Jama 235, 2406. doi:10.1001/jama.1976.03260480026024

Narayan, S.M., Drinan, D.D., Lackey, R.P., Edman, C.F., 2007. Acute volume overload elevates T-wave alternans magnitude. J Appl Physiol 102, 1462–1468. doi:10.1152/japplphysiol.00965.2006

Niederer, S.A., Hunter, P.J., Smith, N.P., 2006. A Quantitative Analysis of Cardiac Myocyte Relaxation: A Simulation Study. Biophys. J. 90, 1697–1722. doi:10.1529/biophysj.105.069534

Noseworthy, P.A., Asirvatham, S.J., 2015. The Knot That Binds Mitral Valve Prolapse and Sudden Cardiac Death. Circulation 132, 551–552. doi:10.1161/CIRCULATIONAHA.115.017979

O'Hara, T., Rudy, Y., 2012. Quantitative comparison of cardiac ventricular myocyte electrophysiology and response to drugs in human and nonhuman species. Am. J. Physiol. Heart Circ. Physiol. 302, H1023-30. doi:10.1152/ajpheart.00785.2011

Opthof, T., Meijborg, V.M.F., Belterman, C.N.W., Coronel, R., 2015. Synchronization of repolarization by mechano-electrical coupling in the porcine heart. Cardiovasc. Res. 108, 181–187. doi:10.1093/cvr/cvv140

Opthof, T., Sutton, P., Coronel, R., Wright, S., Kallis, P., Taggart, P., 2012. The association of abnormal ventricular wall motion and increased dispersion of repolarization in humans is independent of the presence of myocardial infarction. Front. Physiol. 3 JUL, 1–10. doi:10.3389/fphys.2012.00235

Orini, M., Taggart, P., Hayward, M., Lambiase, P.D., 2017. Spatiotemporal characterization of the transition from sinus rhythm to ventricular fibrillation during an acute ischemic event in the intact human heart by whole-heart sock-mapping. Hear. Case Reports 3, 253–257. doi:10.1016/j.hrcr.2017.01.002

Orini, M., Taggart, P., Srinivasan, N., Hayward, M., Lambiase, P.D., 2016. Interactions between Activation and Repolarization Restitution Properties in the Intact Human Heart: In-Vivo Whole-Heart Data and Mathematical Description. PLoS One 11, e0161765. doi:10.1371/journal.pone.0161765

Parker, K.K., 2004. Stretch-induced ventricular arrhythmias during acute ischemia and reperfusion. J. Appl. Physiol. 97, 377–383. doi:10.1152/japplphysiol.01235.2001

Pastore, J.M., Girouard, S.D., Laurita, K.R., Akar, F.G., Rosenbaum, D.S., 1999. Mechanism linking T-wave alternans to the genesis of cardiac fibrillation. Circulation 99, 1385–1394. doi:10.1161/01.CIR.99.10.1385

Pennington, J.E., Taylor, J., Lown, B., 1970. Chest Thump for Reverting Ventricular Tachycardia. N. Engl. J. Med. 283, 1192–1195. doi:10.1056/NEJM197011262832204

Peyronnet, R., Nerbonne, J.M., Kohl, P., 2016. Cardiac Mechano-Gated Ion Channels and Arrhythmias. Circ. Res. 118, 311–329. doi:10.1161/CIRCRESAHA.115.305043

Pogwizd, S.M., Corr, P.B., 1987. Reentrant and nonreentrant mechanisms contribute to arrhythmogenesis during early myocardial ischemia: results using three-dimensional

mapping. Circ. Res. 61, 352–71.

Prinzen, F.W., Hunter, W.C., Wyman, B.T., McVeigh, E.R., 1999. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. J. Am. Coll. Cardiol. 33, 1735–42. doi:10.1016/S0735-1097(99)00068-6

Pueyo, E., Orini, M., Rodríguez, J.F., Taggart, P., 2016. Interactive effect of beta-adrenergic stimulation and mechanical stretch on low-frequency oscillations of ventricular action potential duration in humans. J. Mol. Cell. Cardiol. 97, 93–105. doi:10.1016/j.yjmcc.2016.05.003

Quinn, T.A., 2014. The importance of non-uniformities in mechano-electric coupling for ventricular arrhythmias. J. Interv. Card. Electrophysiol. 39, 25–35. doi:10.1007/s10840-013-9852-0

Quinn, T.A.A., Kohl, P., 2013. Combining wet and dry research: Experience with model development for cardiac mechano-electric structure-function studies. Cardiovasc. Res. 97, 601–611. doi:10.1093/cvr/cvt003

Quinn, T.A., Kohl, P., 2016. Rabbit models of cardiac mechano-electric and mechano-mechanical coupling. Prog. Biophys. Mol. Biol. 121, 110–122. doi:10.1016/j.pbiomolbio.2016.05.003

Quinn, T.A., Kohl, P., Ravens, U., 2014. Cardiac mechano-electric coupling research: Fifty years of progress and scientific innovation. Prog. Biophys. Mol. Biol. 115, 71–75. doi:10.1016/j.pbiomolbio.2014.06.007

Quintanilla, J.G., Moreno, J., Archondo, T., Usandizaga, E., Molina-Morúa, R., Rodríguez-Bobada, C., González, P., García-Torrent, M.J., Filgueiras-Rama, D., Pérez-Castellano, N., Macaya, C., Pérez-Villacastín, J., 2015. Increased intraventricular pressures are as harmful as the electrophysiological substrate of heart failure in favoring sustained reentry in the swine heart. Heart Rhythm 12, 2172–83. doi:10.1016/j.hrthm.2015.05.017

Radszuweit, M., Alvarez-Lacalle, E., Bär, M., Echebarria, B., 2015. Cardiac contraction induces discordant alternans and localized block. Phys. Rev. E. Stat. Nonlin. Soft Matter Phys. 91, 22703. doi:10.1103/PhysRevE.91.022703

Ravelli, F., Disertori, M., Cozzi, F., Antolini, R., Allessie, M.A., 1994. Ventricular beats induce variations in cycle length of rapid (type II) atrial flutter in humans. Evidence of leading circle reentry. Circulation 89, 2107–2116. doi:10.1161/01.CIR.89.5.2107

Ravelli, F., Masè, M., Del Greco, M., Marini, M., Disertori, M., 2011. Acute atrial dilatation slows conduction and increases AF vulnerability in the human atrium. J. Cardiovasc. Electrophysiol. 22, 394–401. doi:10.1111/j.1540-8167.2010.01939.x

Ravelli, F., Masè, M., Disertori, M., 2008. Mechanical modulation of atrial flutter cycle length. Prog. Biophys. Mol. Biol. 97, 417–434. doi:10.1016/j.pbiomolbio.2008.02.018

Ravens, U., 2003. Mechano-electric feedback and arrhythmias. Prog. Biophys. Mol. Biol. 82, 255–266. doi:10.1016/S0079-6107(03)00026-9

Reiter, M.J., 1996. Effects of mechano-electrical feedback: potential arrhythmogenic influence in patients with congestive heart failure. Cardiovasc. Res. 32, 44–51.

Reiter, M.J., Landers, M., Zetelaki, Z., Kirchhof, C.J.H., Allessie, M.A., 1997. Electrophysiological Effects of Acute Dilatation in the Isolated Rabbit Heart. Circulation 96, 4050–4056.

Reiter, M.J., Stromberg, K.D., Whitman, T.A., Adamson, P.B., Benditt, D.G., Gold, M.R., 2013. Influence of intracardiac pressure on spontaneous ventricular arrhythmias in patients with systolic heart failure: Insights from the REDUCEhf trial. Circ. Arrhythmia Electrophysiol. 6, 272–278. doi:10.1161/CIRCEP.113.000223

Rosenbaum, D.S., Jackson, L.E., Smith, J.M., Garan, H., Ruskin, J.N., Cohen, R.J., 1994. Electrical alternans and vulnerability to ventricular arrhythmias. N. Engl. J. Med. 330, 235–41. doi:10.1056/NEJM199401273300402

Sarubbi, B., Calvanese, R., Bigazzi, M.C., Santoro, G., Russo, M.G., Calabrò, R., 2004. Electrophysiological changes following balloon valvuloplasty and angioplasty for aortic stenosis and coartaction of aorta: Clinical evidence for mechano-electrical feedback in humans. Int. J. Cardiol. 93, 7–11. doi:10.1016/S0167-5273(03)00147-5

Sauer, A., Wilcox, J.E., Andrei, A.-C.C., Passman, R., Goldberger, J.J., Shah, S.J., 2012. Diastolic electromechanical coupling: Association of the ecg t-peak to t-end interval with echocardiographic markers of diastolic dysfunction. Circ. Arrhythmia Electrophysiol. 5, 537–543. doi:10.1161/CIRCEP.111.969717

Selvaraj, R.J., Suszko, A., Subramanian, A., Mak, S., Wainstein, R., Chauhan, V.S., 2011. Microscopic systolic pressure alternans in human cardiomyopathy: Noninvasive evaluation of a novel risk marker and correlation with microvolt T-wave alternans. Heart Rhythm 8, 236–243. doi:10.1016/j.hrthm.2010.10.013

Seo, K., Inagaki, M., Nishimura, S., Hidaka, I., Sugimachi, M., Hisada, T., Sugiura, S., 2010.

Structural heterogeneity in the ventricular wall plays a significant role in the initiation of stretch-induced arrhythmias in perfused rabbit right ventricular tissues and whole heart preparations. Circ. Res. 106, 176–184. doi:10.1161/CIRCRESAHA.109.203828

Siogas, K., Pappas, S., Graekas, G., Goudevenos, J., Liapi, G., Sideris, D. a, 1998. Segmental wall motion abnormalities alter vulnerability to ventricular ectopic beats associated with acute increases in aortic pressure in patients with underlying coronary artery disease. Heart 79, 268–73.

Solovyova, O., Katsnelson, L.B., Kohl, P., Panfilov, A. V., Tsaturyan, A.K., Tsyvian, P.B., 2016. Mechano-electric heterogeneity of the myocardium as a paradigm of its function. Prog. Biophys. Mol. Biol. 120, 249–254. doi:10.1016/j.pbiomolbio.2015.12.007

Solovyova, O., Katsnelson, L.B., Konovalov, P. V., Kursanov, A.G., Vikulova, N.A., Kohl, P., Markhasin, V.S., 2014. The cardiac muscle duplex as a method to study myocardial heterogeneity. Prog. Biophys. Mol. Biol. doi:10.1016/j.pbiomolbio.2014.07.010

Sosunov, E.A., Anyukhovsky, E.P., Rosen, M.R., 2008. Altered ventricular stretch contributes to initiation of cardiac memory. Heart Rhythm 5, 106–113. doi:10.1016/j.hrthm.2007.09.008

Srinivasan, N.T., Orini, M., Simon, R.B., Providência, R., Khan, F., Segal, O.R., Babu, G., Bradley, R., Rowland, E., Ahsan, S., Chow, A.W., Lowe, M., Taggart, P., Lambiase, P., 2016. Ventricular Stimulus Site Influences Dynamic Dispersion of Repolarization In The Intact Human Heart. Am. J. Physiol. - Hear. Circ. Physiol. ajpheart.00159.2016. doi:10.1152/ajpheart.00159.2016

Stacy, G.P., Jobe, R.L., Taylor, L.K., Hansen, D.E., 1992. Stretch-induced depolarizations as a trigger of arrhythmias in isolated canine left ventricles. Am. J. Physiol. - Hear. Circ. Physiol. 263, H613–H621.

Stevenson, W.G., Khan, H., Sager, P., Saxon, L.A., Middlekauff, H.R., Natterson, P.D., Wiener, I., 1993. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction 88, 1647–1670.

Sung, D., Mills, R.W., Schettler, J., Narayan, S.M., Omens, J.H., McCulloch, A.D., 2003. Ventricular filling slows epicardial conduction and increases action potential duration in an optical mapping study of the isolated rabbit heart. J Cardiovasc Electrophysiol 14, 739–749. doi:10.1046/j.1540-8167.2003.03072.x

Sutton, P.M., Taggart, P., Lab, M., Runnalls, M.E., O'Brien, W., Treasure, T., 1991. Alternans

of epicardial repolarization as a localized phenomenon in man. Eur. Heart J. 12, 70–8.

Suzuki, T., Nazarian, S., Jerosch-Herold, M., Chugh, S.S., 2016. Imaging for assessment of sudden death risk: current role and future prospects. Europace 18, 1491–1500. doi:10.1093/europace/euv456

Taggart, P., 1996. Mechano-electric feedback in the human heart. Cardiovasc. Res. 32, 38–43. doi:10.1016/0008-6363(95)00240-5

Taggart, P., Lab, M., 2008. Cardiac mechano-electric feedback and electrical restitution in humans. Prog. Biophys. Mol. Biol. 97, 452–460. doi:10.1016/j.pbiomolbio.2008.02.021

Taggart, P., Orini, M., Hanson, B., Hayward, M., Clayton, R., Dobrzynski, H., Yanni, J., Boyett, M., Lambiase, P.D.P.D., 2014. 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. Prog. Biophys. Mol. Biol. 115, 252–260. doi:10.1016/j.pbiomolbio.2014.06.004

Taggart, P., Sutton, P., John, R., Lab, M., Swanton, H., 1992a. Monophasic action potential recordings during acute changes in ventricular loading induced by the Valsalva manoeuvre. Br. Heart J. 67, 221–9.

Taggart, P., Sutton, P., Lab, M., Runnalls, M., O'Brien, W., Treasure, T., 1992b. Effect of abrupt changes in ventricular loading on repolarization induced by transient aortic occlusion in humans. Am. J. Physiol. 263, H816-23.

Taggart, P., Sutton, P.M.I., 1999. Cardiac mechano-electric feedback in man: clinical relevance. Prog. Biophys. Mol. Biol. 71, 139–154. doi:10.1016/S0079-6107(98)00039-X

Taggart, P., Sutton, P.M.I., Treasure, T., Lab, M., O'Brien, W., Runnalls, M., Swanton, R.H., Emanuel, R.W., 1988. Monophasic action potentials at discontinuation of cardiopulmonary bypass: Evidence for contraction-excitation feedback in man. Circulation 77, 1266–1275. doi:10.1161/01.CIR.77.6.1266

Thomsen, M.B., Volders, P.G.A., Beekman, J.D.M., Matz, J., Vos, M.A., 2006. Beat-to-Beat Variability of Repolarization Determines Proarrhythmic Outcome in Dogs Susceptible to Drug-Induced Torsades de Pointes. J. Am. Coll. Cardiol. 48, 1268–1276. doi:10.1016/j.jacc.2006.05.048

Toschi, N., Canichella, A., Coniglione, F., Sabato, E., della Badia Giussi, F., Dauri, M., Sabato, A.F., Guerrisi, M.G., Ferrario, M., Aletti, F., Signorini, M.G., Baselli, G., Cerutti, S., 2010. Intraoperative haemodynamic monitoring: A pilot study on integrated data collection,

processing and modelling for extracting vital signs and beyond, in: 2010 3rd International Symposium on Applied Sciences in Biomedical and Communication Technologies (ISABEL 2010). IEEE, pp. 1–5. doi:10.1109/ISABEL.2010.5702766

Trayanova, N. a, Constantino, J., Gurev, V., 2011. Electromechanical models of the ventricles. Am. J. Physiol. Heart Circ. Physiol. 301, H279–H286. doi:10.1152/ajpheart.00324.2011

van Duijvenboden, S., Hanson, B., Child, N., Orini, M., Rinaldi, C.A., Gill, J., Taggart, P., 2015. Effect of autonomic blocking agents on the respiratory related oscillations of ventricular action potential duration in humans. Am. J. Physiol. Heart Circ. Physiol. 309, ajpheart.00560.2015. doi:10.1152/ajpheart.00560.2015

Veire, N.R.L. Van de, Bax, J.J., 2011. Evidence for mechano-electric coupling from clinical trials on cardiac resynchronization therapy, in: Peter Kohl, Frederick Sachs, and M.R.F. (Ed.), Cardiac Mechano-Electric Coupling and Arrhythmias (2 Ed.). "Oxford University Press," Oxford, UK. doi:10.1093/med/9780199570164.003.0058

Walters, T.E., Lee, G., Spence, S., Larobina, M., Atkinson, V., Antippa, P., Goldblatt, J., O'Keefe, M., Sanders, P., Kistler, P.M., Kalman, J.M., 2014. Acute atrial stretch results in conduction slowing and complex signals at the pulmonary vein to left atrial junction: Insights into the mechanism of pulmonary vein arrhythmogenesis. Circ. Arrhythmia Electrophysiol. 7, 1189–1197. doi:10.1161/CIRCEP.114.001894

Waxman, M.B., Yao, L., Cameron, D.A., Kirsh, J.A., 1991. Effects of posture, Valsalva maneuver and respiration on atrial flutter rate: An effect mediated through cardiac volume. J. Am. Coll. Cardiol. 17, 1545–1552. doi:10.1016/0735-1097(91)90645-P

Weiss, J.N., Garfinkel, A., Karagueuzian, H.S., Nguyen, T.P., Olcese, R., Chen, P.S., Qu, Z., 2015. Perspective: A dynamics-based classification of ventricular arrhythmias. J. Mol. Cell. Cardiol. 82, 136–152. doi:10.1016/j.yjmcc.2015.02.017

Wolk, R., 2000. Arrhythmogenic mechanisms in left ventricular hypertrophy. Europace 2, 216–223. doi:10.1053/eupc.2000.0110

Xu, L., Gutbrod, S.R., Bonifas, A.P., Su, Y., Sulkin, M.S., Lu, N., Chung, H.-J., Jang, K.-I., Liu, Z., Ying, M., Lu, C., Webb, R.C., Kim, J.-S., Laughner, J.I., Cheng, H., Liu, Y., Ameen, A., Jeong, J.-W., Kim, G.-T., Huang, Y., Efimov, I.R., Rogers, J.A., 2014. 3D multifunctional integumentary membranes for spatiotemporal cardiac measurements and stimulation across the entire epicardium. Nat. Commun. 5, 3329. doi:10.1038/ncomms4329

Yapari, F., Deshpande, D., Belhamadia, Y., Dubljevic, S., 2014. Control of cardiac alternans

by mechanical and electrical feedback. Phys. Rev. E 90, 12706. doi:10.1103/PhysRevE.90.012706

Zabel, M., Koller, B., Sachs, F., Franz, M., 1996a. Stretch-induced voltage changes in the isolated beating heart: Importance of the timing of stretch and implications for stretch-activated ion channels. Cardiovasc. Res. 32, 120–130. doi:10.1016/0008-6363(96)00089-2

Zabel, M., Portnoy, S., Franz, M.R., 1996b. Effect of sustained load on dispersion of ventricluar repolarization and conduction time in the isolated intact rabbit heart. J. Cardiovasc. Electrophysiol. 7, 9–16. doi:10.1111/j.1540-8167.1996.tb00455.x

Zhou, X., Bueno-Orovio, A., Orini, M., Hanson, B., Hayward, M., Taggart, P., Lambiase, P.D., Burrage, K., Rodriguez, B., 2016. In Vivo and in Silico Investigation into Mechanisms of Frequency Dependence of Repolarization Alternans in Human Ventricular Cardiomyocytes. Circ. Res. 118, 266–278. doi:10.1161/CIRCRESAHA.115.307836

Zhu, W.-X., Johnson, S.B., Brandt, R., Burnett, J., Packer, D.L., 1997. Impact of Volume Loading and Load Reduction on Ventricular Refractoriness and Conduction Properties in Canine Congestive Heart Failure. J. Am. Coll. Cardiol. 30, 825 LP-833.

Figures

Figure 1

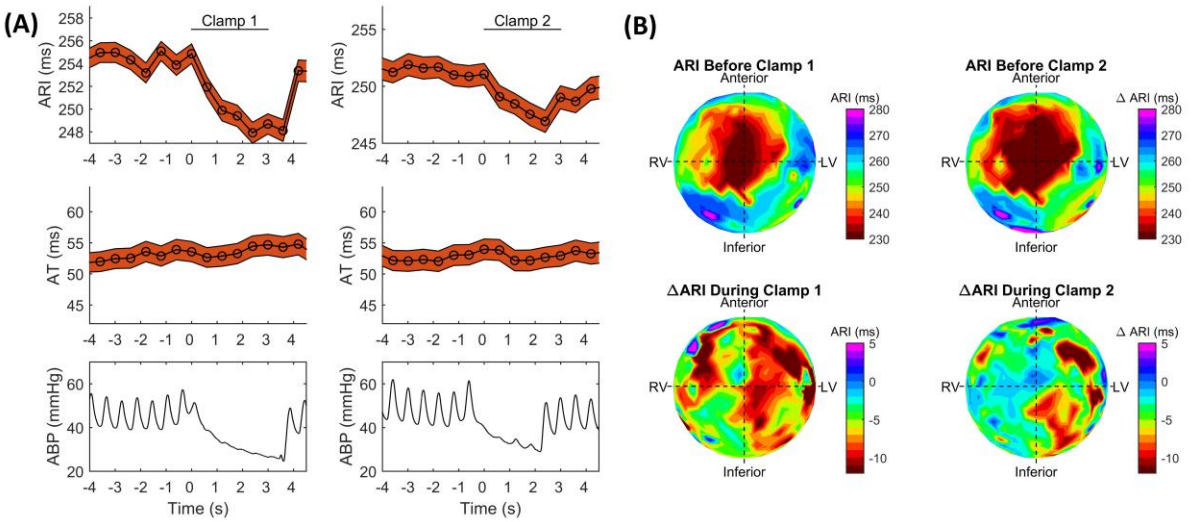

Figure 2

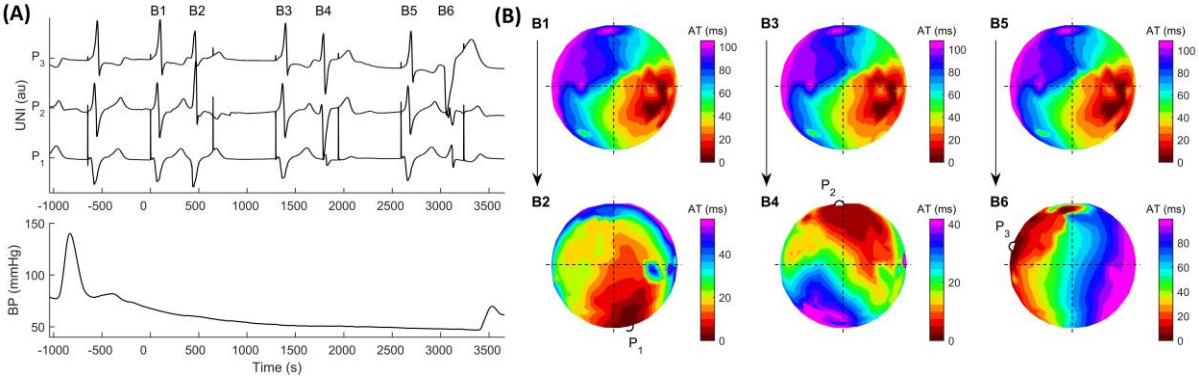

Figure 3

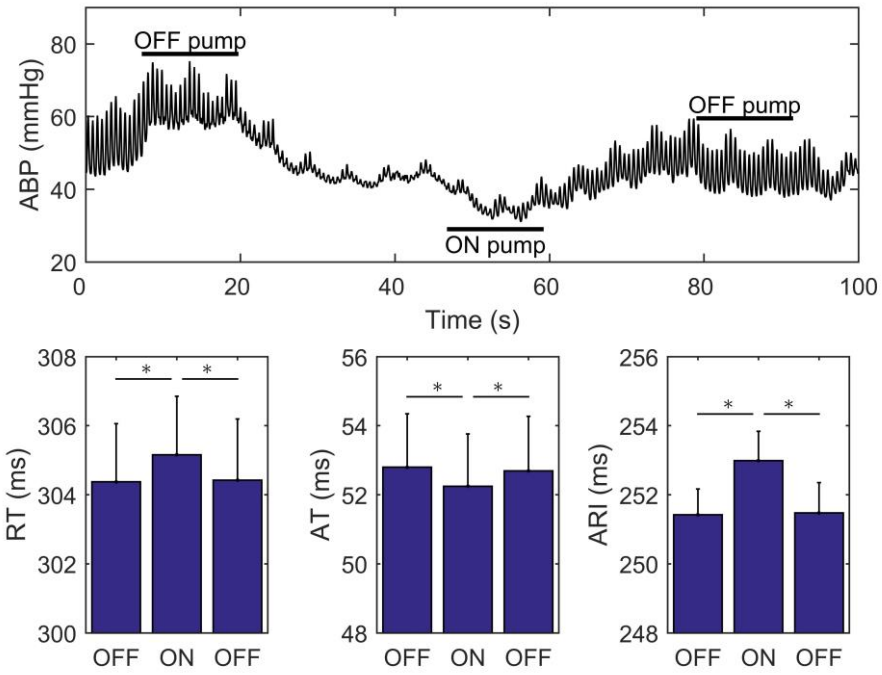

Figure 4