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Original Research

Mechano-electric coupling, heterogeneity in repolarization and the electrocardiographic T-wave

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ABSTRACT

Stretch influences repolarization by mechano-electric coupling (MEC) and contributes to arrhythmogenesis. Although there is an abundance of research on electrophysiological effects of MEC, it is still unclear how MEC translates to the ECG. We aim to provide an overview of the MEC research focused on the ECG and the underlying changes in electrophysiology. In addition, we present new data on the effect of left ventricular pressure on the electrocardiographic T-wave. We show that an increase in left ventricular pressure leads to prolonged QT-intervals with increased amplitudes of the STT-segment. This corresponds to a prolongation in repolarization and an increased interventricular dispersion of repolarization. MEC is dependent on timing, intensity and modality of stretch and these three factors should be taken into account to analyse the effects of MEC on the heart and on the ECG. In addition, the deformation of the heart itself should be considered, since it influences the amplitude of the STT-segment. Because the electrocardiographic T-wave represents heterogeneity in repolarization, left ventricular pressure increases may have significant influence on the inducibility of (re-entrant) arrhythmias.

1. Introduction

Heart failure is associated with ventricular overload and increased end-diastolic LV pressure (Shub, 1989), and leads to stretch in the ventricular wall. Stretch – through mechano-electric coupling (MEC) – has effect on the ventricular action potential (Taggart and Sutton, 1999). Acute elevations in cardiac pressure and volume can therefore lead to altered cardiac electrophysiology (Taggart and Sutton, 1999), and may be arrhythmogenic (Hansen et al., 1990). If loading conditions become chronic, electrical and structural remodelling occur, making the heart even more vulnerable to arrhythmias (Coronel et al., 2013; Tomaselli and Zipes, 2004). It has been suggested that remodelled hearts are also more sensitive to physiological changes in ventricular loading (Taggart et al., 1992a). Indeed, heart failure is also associated with sudden cardiac death (Coronel et al., 2013; Kjekshus, 1990).

Many studies have been conducted to explore the acute effects of MEC (Lab, 1982; Taggart and Sutton, 1999) and the role in the induction of arrhythmias (Janse et al., 2003). Most studies have focused on changes measured at the cellular or tissue level and results have shown mainly an effect on (dispersion of) repolarization, which is an important factor in arrhythmogenesis (Han and Moe, 1964). The ECG is recorded from the body surface and is expected to reflect these stretch-induced changes in repolarization (Noble and Cohen, 1978). However, systematic studies on the relation between stretch and the ECG are scarce. The knowledge about the MEC effects on the ECG is important in the clinical setting of hemodynamic changes. Therefore, we provide an overview of the effects of MEC on the ECG in relation to the underlying changes in electrophysiology. Within this perspective we also show novel data on pressure-induced ECG changes.

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2. MEC effect on electrophysiology

Cardiac MEC - originally labelled as 'mechano-electric feedback' – describes the mechanism by which mechanical action exerted on and/or by the heart leads to altered cardiac electrophysiology, which may initiate a fatal arrhythmia (i.e. commotio cordis) (Kohl et al., 2001). Since Max Lab described the phenomenon of MEC in frog hearts (Lab, 1978), major progress has been made in MEC research (Quinn et al., 2014). At the cellular and tissue level, several experimental studies have been conducted to explore the electrophysiological effects of a multitude of mechanical perturbations (e.g. shrinking or swelling (Baumgarten and Clemo, 2003), compression or stretching (Isenberg et al., 2003), intraventricular fluid injections (Lab, 1978) and mechanical impact (Kohl et al., 2001)). The results demonstrated mostly a shortening of action potential duration or refractoriness during stretch (Levine et al., 1988; Taggart et al., 1992b). In contrast, there have been also some studies that have shown opposite effects (Benditt et al., 1985; Taggart et al., 1992a). These discrepancies may be explained by differences in the type of stretch imposed; isometric (i.e. aortic clamping or valvuloplasty) versus isotonic contraction (i.e. unloading due to Valsalva manoeuvre), on which we elaborate later in this review. Also species differences (human versus dog), methodological differences (monophasic action potentials versus refractory periods), differences in pacing conditions (atrial pacing with ventricular extrastimuli versus sinus rhythm or atrial pacing), or intensity and timing of pressure/volume (afterload versus preload) could have led to opposite effects.

Also, depolarization of the membrane potential may occur as a result of end-systolic or diastolic stretch pulses, which may lead to afterdepolarizations and/or premature beats with increasing amplitude of the stretch pulse (Franz et al., 1992; Haemers et al., 2015; Lab, 1978; Zabel et al., 1996). In some cases this can result in non-sustained arrhythmias (Hansen et al., 1990). For an extensive overview of the basics of MEC effects we refer to the existing literature (Franz, 1996; Kohl and Ravens, 2003; Lab, 1982; Taggart and Sutton, 1999).

MEC is mediated by stretch-activated channels, i.e. non-specific cation channels that activate by membrane stretch. These stretch activated channels (SACs) were first described in skeletal muscle (Guharay and Sachs, 1984). Later, SACs were also described in cardiac muscle, having a reversal potential of about 30 mV less negative than the resting membrane potential (Craelius et al., 1988). It was suggested that this reversal potential could explain the differences in reported responses in action potential duration or refractoriness to stretch (Zabel et al., 1996). Therefore, depending on the timing of stretch relative to the phase of the action potential, activation of the SACs theoretically results either in a repolarizing (outward) or depolarizing (inward) ionic current and causes shortening or prolongation of the action potential, respectively. Additionally, the depolarizing current caused by opening of SACs during diastole may cause afterdepolarization that could initiate a new action potential. Data shown by Zabel and colleagues are in line with this hypothesis of crossover effect (Zabel et al., 1996) and fitted with earlier work (Lab, 1978). Fig. 1 is based on data from Zabel et al. 1996 and clearly shows that the stretch effect has a crossover at a membrane potential of approximately - 33 mV. In this figure, we transformed the level of repolarization (defined as % interval from the crest of the AP plateau to complete repolarization) measured by Zabel et al. 1996 to membrane potentials (assuming action potentials repolarizes from +50 mV to −90 mV as simulated by Zabel et al. 1996). This crossover corresponded rather closely with a reversal potential between −20 and −30 mV (Zabel et al., 1996). Recently, we have shown that this time dependent phenomenon even works at physiological pressures and contributes to synchronization of the repolarization moments (Opthof et al., 2015).

The diversity of methodological approaches used and the difficulty in translating the results to a higher level of structural complexity have hampered the definition of the physiological and pathophysiological role of MEC in the intact human heart. A description of how MEC plays a role in the human heart is given by (Taggart, 1996; Taggart and Sutton, 1999). Also in these human studies, the most prominent results were mainly pointing at a shortening of action potential duration or repolarization in response to an increase in ventricular pressure. Although the human studies simulated clinically relevant conditions, the results were complicated by many confounding factors like heart diseases, autonomic influences and ischemic/perfusion deficits due to changed loading. The most solid conclusion is that MEC encompasses a complex phenomenon that depends on the type, intensity and timing of stretch applied (Taggart and Sutton, 1999).

3. MEC effect on the ECG

3.1. Historical

Because a change in stretch results in alterations in repolarization, it is expected that it causes changes in the T-wave on the ECG. In early MEC research there have been some papers that reported about MEC effects on the ECG. In those days, MEC was ascribed to the force-velocity relation of the contracting heart, because a decreased shortening velocity led to a decrease in action potential (AP) duration (Kaufmann et al., 1971). From this perspective, Ford and Campbell hypothesized that the interval between the second heart tone (i.e. closure of aortic valve) and T-wave may indicate the myocardial fibre shortening rate (Ford and Campbell, 1980). They demonstrated that a faster myocardial shortening, induced by amyl nitrate inhalation, resulted in an earlier second heart tone and a longer QT-interval on the ECG after an increase in heart rate when compared to atropine, in which myocardial shortening velocity was unchanged (Ford and Campbell, 1980). However, amyl nitrite resulted also in smaller end-systolic ventricular volumes and accordingly the observed QT prolongation could also be interpreted

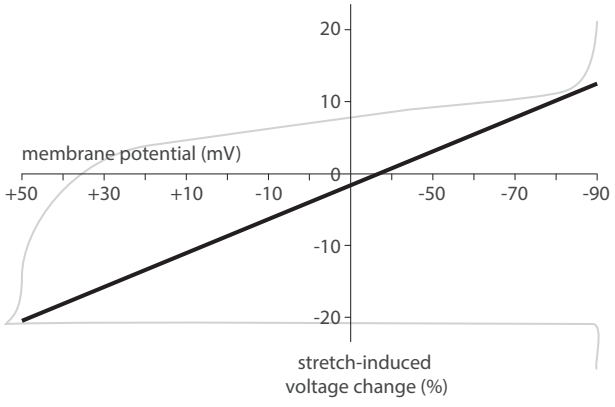

Fig. 1. Crossover effect of MEC.
Plot of stretch-induced voltage changes (in % change of amplitude of monophasic action potential [MAP]) against level of membrane potential, with in grey a schematic action potential. The figure is based on data from the study of Zabel et al. 1996 in which the authors used Langendorff-perfused rabbit hearts. A stretch pulse was applied by injecting an extra volume of 750 μl in a balloon within the left ventricle at different levels of repolarization (% interval from crest of the AP plateau to complete repolarization), during which they measured the change in AP amplitude. We transformed the level of repolarization used in that study into membrane potentials. The crossover effect of repolarization to depolarization occurs at a membrane potential of about −33 mV.

as a result from a decrease in ventricular load. The opposite changes in ventricular loading could also apply to the effects observed by Kaufmann who decreased the shortening velocity by switching from isotonic to isometric contractions, during which an increase in ventricular load can be expected. Lab predicted, by superimposing tracings of action potentials, that during isovolumetric contraction the resulting shortened phase 2 of repolarization in combination with prolonged phase 3 of repolarization (i.e. early afterdepolarization-like) would lead to a lower T-wave amplitude than during auxotonic contraction (Lab, 1978). Indeed, aortic occlusions (i.e. increase in afterload) in the frog led to reduction in T-wave amplitude and T-wave inversion within 6–7 beats with negligible changes in the QRS. (Lab, 1982). Similarly, aortic constriction resulted in smaller T-waves and shortening of the QT-interval in a pig heart (Lab, 1982). In some recordings also a smaller QRS was observed during isovolumetric contraction compared to auxotonic contraction. The smaller QRS was suggested to be the result of reduction in action potential amplitudes (Lab, 1982). It was proposed that the changes in T-wave amplitudes could be explained by the ventricular volume expansion. During normal contraction the endocardial circumference shortens proportionally more, and would therefore experience higher MEC effects than the epicardial circumference. The previous implies that with increasing ventricular volumes the inner and outer circumferences will become less different resulting in similar mechanical conditions for endocardium and epicardium. Although this would lead to similar action potentials and flattened T-waves (Lab, 1978), it cannot explain the QT-interval shortening.

Following the description of stretch-activated channels, the mechanism of MEC could be attributed to stretch applied to the membrane. Based on the early studies on MEC-induced ECG effects, an inverse relation between the QT-interval and ventricular load exists. However, the measured QT-intervals in these studies were mainly measured with either electrodes on the surface of the heart (bipolar or unipolar) or with an electrode submerged in the perfusion fluid close to the heart, which represents a local effect rather than what would be appreciated from the body surface. Levine and colleagues have shown that a similar inverse relation could be observed for the body surface ECG. The authors were able to record RV monophasic action potentials and an ECG simultaneously before and after balloon valvuloplasty for congenital pulmonary stenosis (Levine et al., 1988). An increase in RV pressure, resulting from balloon valvuloplasty of the pulmonary valve, was associated with shortening of the RV action potential duration and of QTc intervals. The opposite prolonging effect was perceived with a fall in RV pressure following the balloon inflation. The QTc prolongation was largest in the patients with the most prominent decrease in RV pressure, although the statistical relation was moderate (Levine et al., 1988).

MEC may heterogeneously alter repolarization (Zabel et al., 1996) even within one cardiac cycle (Opthof et al., 2015). In diseased hearts, when increased loading results in dispersed strain patterns, MEC effects may theoretically result in heterogeneous changes in repolarization within the ventricular wall, and may influence the ECG accordingly (Noble and Cohen, 1978). QT dispersion, defined as the differences between QT-intervals of the same beat among ECG leads, has been proposed to represent the heterogeneity in repolarization process within the heart, and is correlated with an increased risk for arrhythmias (Day et al., 1990). James and colleagues have investigated whether a change in ventricular filling alters QT dispersion (James et al., 2002). They have demonstrated that the QT dispersion increases following a decrease in ventricular filling due to loss of an atrial kick in patients with abnormal LV function. The QT dispersion did not change in patients with a normal LV function. Accordingly, it was suggested that a reduced stretch increases the dispersion in repolarization, but only in patients with abnormal LV function. However, the interpretation of QT dispersion has been under debate, because the relation with the underlying dispersion of repolarization appears to be weak (Liang et al., 2005; Zabel et al., 1995). The T-wave area, T-wave width and T-peak to T-end interval were supposed to be better representations of dispersion in repolarization and may therefore be more reliable measures to represent MEC-induced changes in repolarization (Meijborg et al., 2014; Opthof et al., 2007; Zabel et al., 1995). Overall, we concluded that data of the MEC effect on the surface ECG are sparse, and we did not identify recent attempts to investigate these effects systematically.

4. Study on effect of overload on the ECG

4.1. Introduction

Although previous in vivo studies were performed in clinically relevant situations (i.e. in healthy and diseased humans), the results may have partially been influenced by neurogenic responses or changed coronary perfusion as a consequence of altered pressure and filling. To study the MEC effects on the ECG in absence of these influences we performed experiments in pig hearts perfused on the Langendorff setup, in which we modeled left ventricular (LV) overload by increasing diastolic LV pressure and simultaneously recorded a volume-conducted ECG and epicardial electrograms (Fig. 2).

4.2. Methods

These experiments were approved by the local ethical committee on animal experimentation. Nine pig were premedicated, ventilated and anaesthetized according to the protocol described before (Meijborg et al., 2014).

Experimental setup: the heart was perfused with a 1:1 blood-Tyrode's mixture, and atrial pacing at 650 ms cycle length was performed. We positioned a flexible balloon in the LV, in which diastolic LV pressure was maintained at 0 mmHg (P0) or 20 mmHg (P20) and continuous LV pressure was recorded. Local electrograms were obtained from an epicardial 9 × 12 unipolar electrode sock overlapping the LV and a large part of the right ventricle (RV). The heart with the electrode sock was submerged in a perfusion-fluid filled bucket incorporating 61 regularly distributed electrodes (1 at the bottom) to simultaneously record volume conducted pseudo-ECGs with the assembled average of all 61 electrodes as reference. The apex was fixed to avoid swinging of the heart, but to allow rotation and movement in the vertical plane. In five of the nine hearts we were able to increase the LV diastolic pressure from 0 to 20 mmHg and simultaneously obtain recordings of sufficient quality without pressure-induced ST-segment elevation/depression.

Analyses: in the pseudo-ECGs we determined the maximum *QRS duration* and maximum *QT interval*. *QRSonset* and *QRSend* were defined as the first deflection and last J-point of the QRS complex in any ECG lead, respectively. The *Tend* was determined using the tangent method. Accordingly, in each lead *QRS integrals* and *STT integrals* were calculated defined as area under the QRS and STT (=QRSend-to-Tend) curve. Integral maps were made and dipoles (minimum to maximum integral) were determined. The QRS and STT dipoles were characterized by the vector amplitude (mV) and the vector angles (degrees) in the frontal and transversal plane (the left lateral lead equals 0° and rotation to the anterior/inferior lead denotes a positive angle). We calculated the cross-correlation (P0 vs P20) and the mean of absolute integral differences (P0 vs P20) of the QRS and STT integral maps. In each unipolar epicardial

electrogram we determined activation and repolarization times (ATs and RTs) as before (Coronel et al., 2006) (Fig. 2). Dispersion in repolarization was determined within the entire heart, as well as in the LV and RV region (Fig. 2), as maximum RT minus minimum RT. The interventricular RT dispersion was determined as mean RT in the LV region minus mean RT in the RV region. From the LV pressure recordings we determined the systolic and diastolic pressure (*Psys* and *Pdias*). The moment of halfway peak pressure was determined as the time at 50% of peak pressure relative to the QRS onset as an indication of the start of the pressure pulse.

Statistics: continuous variables were presented as mean ± standard deviation if normally distributed and as median [interquartile range] if not normally distributed. Accordingly, differences between P0 and P20 and between QRS and STT integrals were tested with a paired *t*-test or a Wilcoxon signed-rank test. P-values of $\leq$0.05 were considered as statistically significant.

4.3. Results

We hypothesized that the increased LV pressure changes the T-wave morphology rather than the QRS morphology, because the pressure pulse normally falls after the end of QRS and during the T-wave. Indeed, as shown in the example in Fig. 3, diastolic and systolic LV pressures (Pdias and Psys respectively) were increased after balloon inflation and caused major changes in the T-wave without altering the QRS complex. Generally, a rise in diastolic LV pressure (1 ± 3 to 20 ± 2 mmHg, $P < 0.01$) occurred and was associated with an increase of the systolic pressure from 9 ± 5 to 58 ± 14 mmHg ($P < 0.01$). The moment of halfway peak pressure did not shift in time with respect to QRS onset (109 ± 13 vs, 112 ± 16 ms, $P = 0.77$). QRS duration was not changed significantly (62 ± 12 ms vs, 70 ± 10 ms, $P = 0.06$). The QT-intervals were, however, prolonged (322 ± 18 ms vs, 355 ± 44 ms, $P = 0.05$). In 4 of 5 hearts, the increase in QT-interval was at least 3 times larger than the increase in QRS duration.

To quantify the changes on the (pseudo-)ECG we constructed integral maps with dipole vectors of the QRS and STT-segment. The main direction of the QRS integral dipole vector was leftwards and slightly towards anterolateral, whereas the dipole vector of the STT integral was directed rightwards and slightly towards superior-anterior (Table 1). The example in Fig. 4 clearly demonstrates that when pressure is increased, the pattern in the QRS and STT integral maps does not change, i.e. similar positions of the maxima and minima, similar frontal or transversal angles (arrows, indicating the main direction of vector dipoles) and high cross-correlations (0.98 and 0.97 for QRS and STT respectively) were observed in the absence or presence of pressure. However, the difference maps of the integrals (P20-P0) show that changes in amplitudes of the STT integral are larger (more red and more blue, representing T-waves of larger amplitude) than that of the QRS integral. These results were similar for all hearts (Table 1). Only in 1 out of 5 hearts there was a minor decrease of 3 mVms instead of an increase in STT dipole amplitude. The mean absolute differences of the integral maps between high and low pressure (P20 − P0) were two times larger in the STT integral maps compared to the QRS integral maps. With increased pressure, T-wave maxima and minima enlarge on average by 0.9 mV (i.e. more positive/negative) in 42 of 61 ECG leads, which is consistent with the increase in STT-integral. The other ECG leads showed a decrease of their T-wave maxima and minima.

Epicardial activation and repolarization times (AT and RT, respectively) were determined as before (Coronel et al., 2006). An increase in LV pressure was associated with a slight prolongation (3 ± 2 ms) of the activation times in the LV region, without an effect on AT in the rest of the heart (Table 2). The example in Fig. 5 shows that an increase in LV pressure caused a significant prolongation of repolarization in the LV, without an effect on the RV repolarization (overall data, Table 2). Overall, RT was prolonged with 7 ± 3 ms.

5. Discussion

We show that the increasing LV pressure causes prolongation of the repolarization via mechano-electric coupling in the LV and, consequently, leads to longer QT-intervals and larger STT integrals (i.e. more positive or more negative T-waves).

It is important to emphasize the specific conditions under which these observations were made: 1) an increased (diastolic) loading towards pathophysiological levels, 2) continuous elevation of diastolic pressures, 3) moderately increased systolic pressures (i.e. temporarily during cardiac cycle and relatively low) with fixed timing of the pressure pulse with respect to repolarization, 4) a physiological ventricular conduction (atrial pacing), 5) structurally

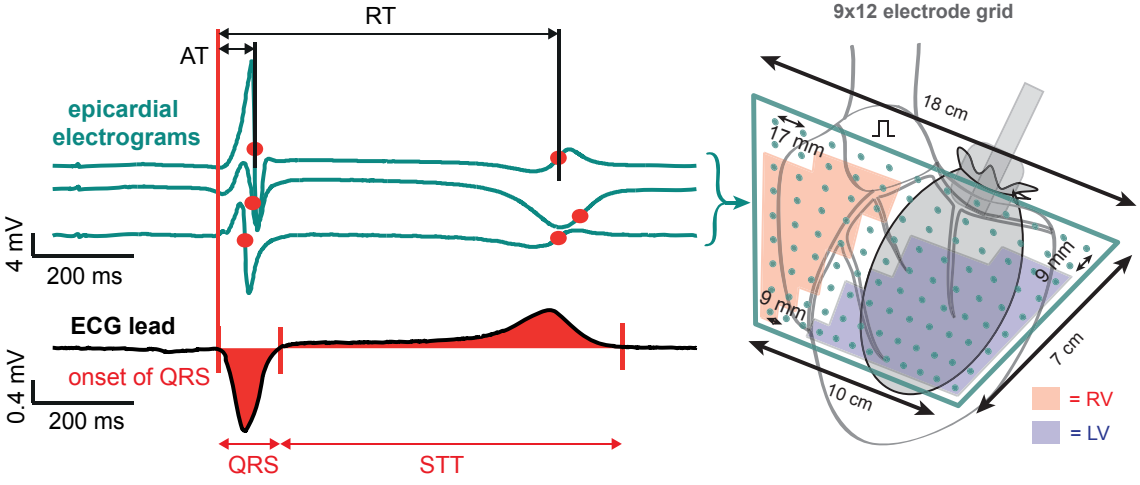

Fig. 2. Experimental setup & measurements.
Experimental setup (right) shows a heart with a flexible balloon positioned in the left ventricle (LV). An epicardial 9 × 12 unipolar electrode sock overlaps the LV and large part of the right ventricle (RV). Electrodes of the RV or LV regions were indicated by the red or blue area respectively. The *block pulse* indicates the position of the pacing lead. Schematic setup of electrophysiologic measurements (left): examples of 3 epicardial electrograms and 1 pseudo-ECG. *Red areas* in the pseudo-ECG lead illustrate the integrals determined for the QRS and STT interval.

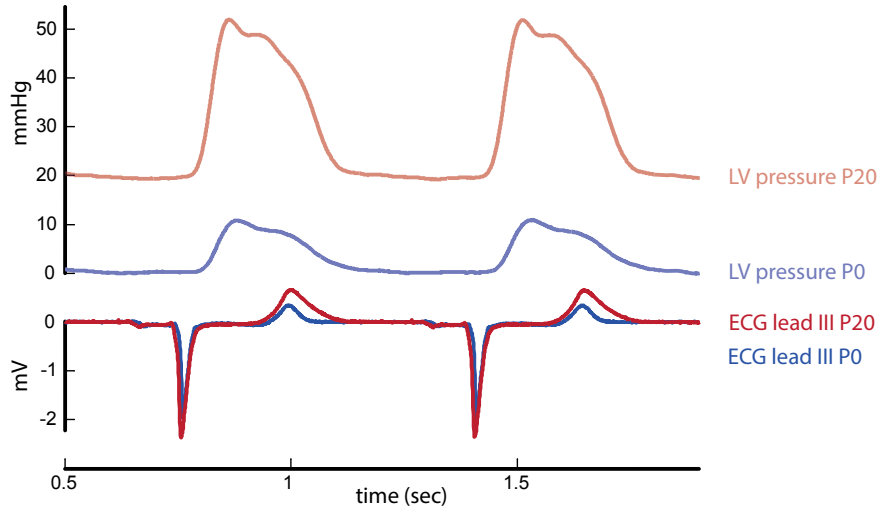

Fig. 3. Pressure-induced ECG changes.
An example of simultaneous recordings of the left ventricular (LV) pressure and ECG lead III at a diastolic LV pressure of 0 mmHg (P0, *blue*) versus 20 mmHg (P20, *red*). The increased diastolic pressure resulted in concomitant changes in the systolic LV pressure and the T-waves.

normal hearts without ventricular remodelling and 6) absence of autonomic influences. MEC effects depend on the timing, intensity and type/modality of stretch and may be categorized to these factors accordingly. Point 2, 3 and 4 are related to timing of stretch, whereas point 1, 2 and 3 are related to intensity and point 1–5 are related to modality (preload, afterload, strain pattern resulting from activation and structure). It is clear that interaction between the three mutually interacting factors complicates the systematic categorization of MEC effects and hampers the comparison between different studies. In order to translate results to clinically relevant situations it is therefore of major importance to consider these three factors and their interaction.

5.1. Three main factors in MEC and their interaction

Fig. 6 shows a schematic classification of MEC and the interactions between the main contributors (MEC triangle). The factor *timing* refers to the duration of the stretch pulse (i.e. temporary versus continuous) (Taggart and Sutton, 1999), as well as the timing of the stretch pulse with respect to the phase of the action potential (Zabel et al., 1996). This timing factor is heterogeneous within the heart during one cycle (Opthof et al., 2015) as a result of intrinsic dispersion in activation and repolarization relative to the pressure pulse. The *intensity* indicates the extent of change in stretch (physiological or pathophysiological). The *modality* of stretch points to the type of deformation (i.e. basic elements of stretch, compression, bending or shearing) that leads to a stress-strain distribution within the heart. In the human heart a single modality rarely occurs in isolation. For example, altered preload or afterload could result in combinations of stretching, compression, shearing or bending, which may be dependent on the presence of structurally altered tissue (e.g. infarcted tissue, fibrosis). Each type of deformation may lead to different stress-strain relations.

An increased preload during diastolic acute heart failure, for example, concerns changes during diastole (timing) at pathophysiological high levels (intensity). Also, the modality is of importance; dilated cardiomyopathy may primarily lead to stretching while hypertrophic cardiomyopathy may primarily cause compression. Alternatively, there is reduced preload during a premature ventricular beat, leading to an unphysiological lower volume and pressure (intensity) during diastole (timing) and to more bending and less stretching (modality). The contraction following a premature activation generally results in a higher volume and pressure, with less bending and more stretching.

MEC during chronic stretch is complicated by ventricular remodelling, such as fibrosis and altered ion channel gene expression. In that way, the chronic stretch may result in an arrhythmogenic substrate of the heart (Opthof et al., 2012). The remodelling influences the interaction of the three factors and could cause a heterogeneity in MEC between various regions of the heart (Fig. 6). The arrhythmogenic substrate may thus result in dispersed strain patterns leading to heterogeneous ***MEC modalities*** (e.g. enlarged pre-stretch and shear in the border zone of the infarct area and bending within the fibrotic zone due to bulging) and heterogeneous ***MEC intensity*** (stress in fibrotic wall will probably be higher than stress in unaffected regions). In addition, due to the remodelling the dispersion in repolarization may also be increased inducing a heterogeneous ***MEC timing*** of the stretch with respect to the repolarization phase.

Table 1
Characteristics of the integral maps (mean ± SD).

	P0	P20	*P* value
QRSint			
A dipole, mV	65 ± 15	76 ± 12	0.02[a1]
Vf dipole, degree	−12 [−62–1]	−12 [−62–−12]	0.32[b1]
Vt dipole, degree	−9 [−9–59]	−9 [−9–41]	0.32[b1]
Xcorr map	0.99 [0.98–1.00]		
Δint map, mVms	3.26 ± 1.36		
STTint			
A dipole, mV	55 ± 22	71 ± 19	0.05[a1]
Vf dipole, degree	−150 [−158–−130]	−150 [−158–−85]	0.18[b1]
Vt dipole, degree	161 [139–212]	161 [53–212]	0.18[b1]
Xcorr map	0.97 [0.73–0.98]	0.07[b2]	
Δint map, mVms	6.52 ± 2.56		0.04[a2]

QRSint = integral map of QRS interval; STTint = integral map of STT interval; dipoles characterized by the vector amplitude (*A dipole*, in mV) and the vector angles (degrees) in the frontal (*Vf dipole*) and transversal plane (*Vt dipole*, the left lateral lead equals 0° and rotation to the anterior/inferior lead denotes a positive angle); Xcorr = cross-correlation of QRSint or STTint between P0 and P20 in mean (min – max); Δint = mean of absolute differences (P20 − P0) of QRSint or STTint.
P values are given for [a] paired *t*-test or [b] Wilcoxon signed-rank test: [1] P0 versus P20; [2] QRSint versus STTint.

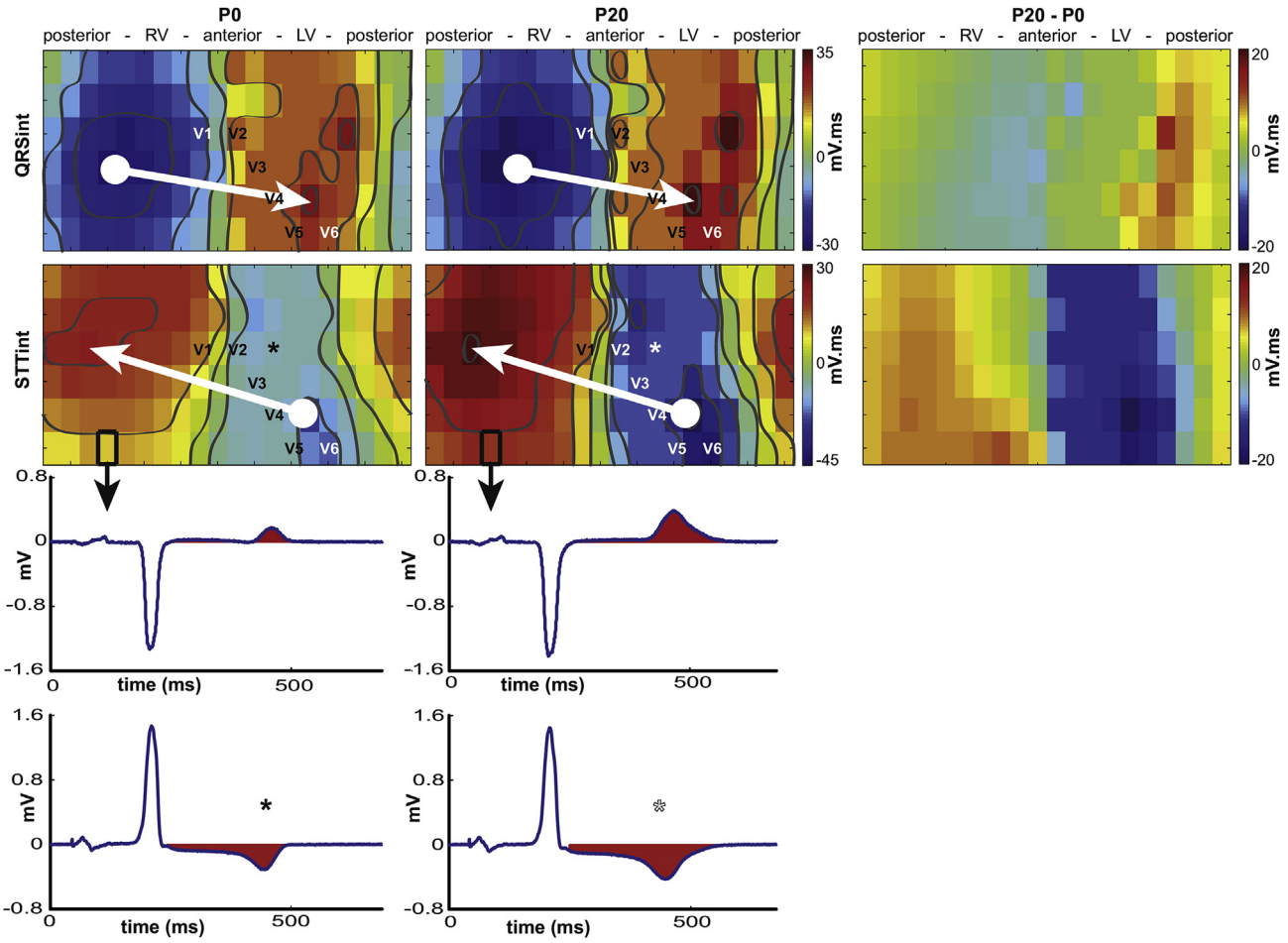

Fig. 4. QRS and STT integral maps.
A typical example of QRS and STT integral maps with dipole vectors (*white arrows*) and isointegral lines (*grey*, 10 mVms distance) and two ECG lead (from the site indicated with the *black boxes* and the *asterisks*) during P0 (left) and P20 (middle). Difference maps (P20 − P0) of the QRS and STT integrals are shown on the right.

5.2. The results in perspective of the MEC triangle

Because systolic stretch (during the AP plateau or repolarization phase) has been shown to influence repolarization (Zabel et al., 1996), increased pressure during systole is the main factor explaining the prolonged repolarization and QT-interval and increased STT-integrals, with augmented T-wave maxima and minima in the majority of ECG leads (see our study above). Earlier reports did, however, show a reduction in T-wave amplitude and QT-interval during increased systolic pressures (Lab, 1982, 1978; Levine et al., 1988). The discrepancy may be ascribed to differences in intensity since these reports used pathophysiological, high systolic pressures. Moreover, in our study also diastolic pressure was increased. This may explain the small and non-significant prolonged activation time and the increase in integral amplitudes of the QRS complex due to depolarization of the membrane (Franz et al., 1992). It could be argued that the activation delay explains the prolonged repolarization times, but prolongation of repolarization was about three times larger than activation delay. Theoretically, the increase in diastolic pressure is less likely to have an effect on repolarization, although at the end of the contraction wave it may still result in afterdepolarization-like prolonged repolarization. This latter may even explain why the observed prolongation of repolarization time (+7 ms) was relatively small compared to the QT prolongation (+34 ms). The proposed mechanism is schematically depicted in Fig. 7B together with two other potential mechanism of ST-changes based on small RT changes (Fig. 7A and C). The first two situations illustrate the small shift in RT by AP prolongation both with a steep repolarization phase. In Fig. 7A heterogeneous and small pressure-induced RT prolongations without AP morphology

Table 2
Characteristics of epicardial electrograms (mean ± SD).

N = 5	P0	P20	*P* value
AT max, ms	57 ± 12	61 ± 11	0.14
AT total, ms	32 ± 8	35 ± 6	0.06
AT_LV, ms	37 ± 12	41 ± 10	0.04
AT_RV, ms	21 ± 3	21 ± 4	0.75
RT total, ms	247 ± 19	253 ± 21	0.02
RT_LV, ms	258 ± 21	267 ± 24	0.02
RT_RV, ms	227 ± 19	229 ± 18	0.20
dRT total, ms	73 ± 15	90 ± 14	0.01
dRT_LV, ms	45 ± 13	56 ± 18	0.12
dRT_RV, ms	48 ± 12	55 ± 13	0.22
dRT_inter, ms	31 ± 10	38 ± 12	0.06

N = number of hearts, AT max = maximum AT; AT = average of mean AT per heart; RT = average of mean RT per heart; total, LV and RV indicate the sets of electrodes used to determine values; dRT = average of RTmax-RTmin per heart (for total, LV and RV). dRT_inter = average of mean RT_LV − mean RT_RV.
P values are given for paired t tests.
Activation times was determined on 73 ± 9 electrodes in total, of which 43 ± 4 electrodes were in the LV region and 19 ± 3 electrodes in the RV region.
Repolarization times was determined on 59 ± 7 electrodes in total, of which 33 ± 5 electrodes were in the LV region and 16 ± 3 electrodes in the RV region.

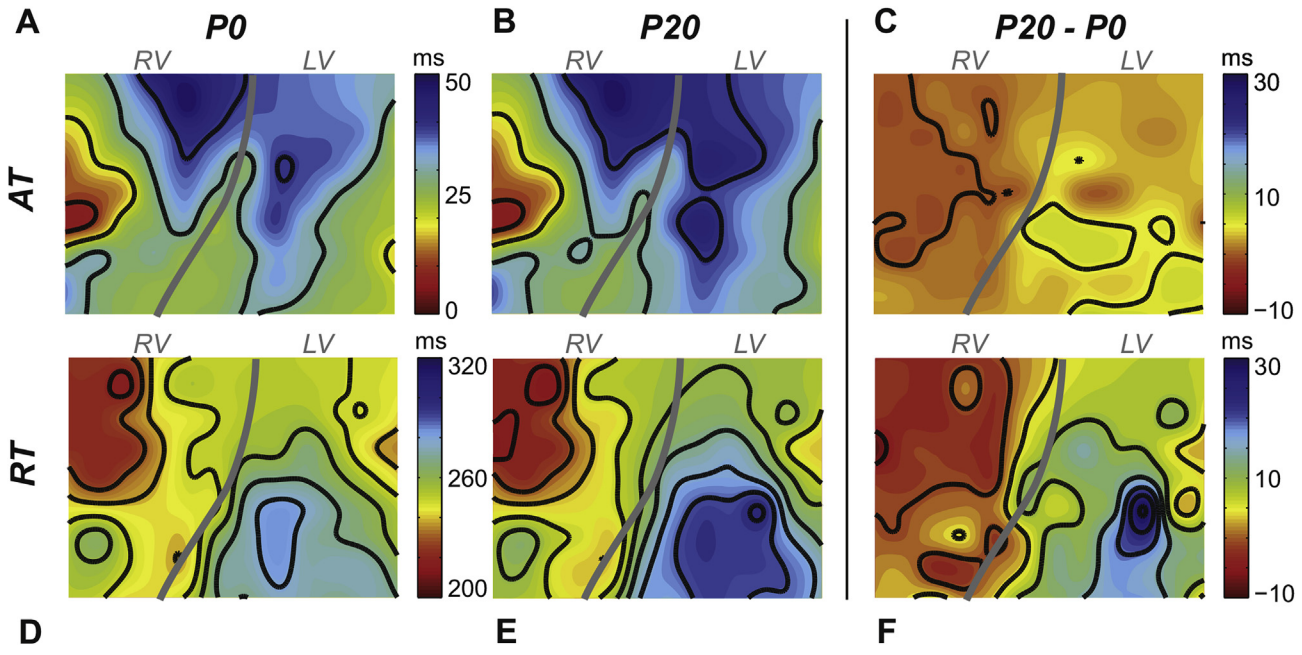

Fig. 5. Activation and repolarization maps.
Upper panels: Activation time (AT) maps during P0 (A) and P20 (B) and AT difference map P20 − P0 (C). Activation starts in the anterolateral region of the RV and is followed by the LV and is latest in the anterior RV base. Slight changes in activation were observed during an increased LV pressure. Lower panels: Repolarization time (RT) maps during P0 (D) and P20 (E) and RT difference map P20 − P0 (F). Repolarization is earliest at the RV base and latest in the LV apex. The pattern remained similar during high pressure, although RT increased. Isochrones (*black lines*) are at 10 ms intervals in the AT and RT maps, and at 5 ms intervals in the difference maps. *Grey line* indicates the septal border between RV and LV.

change lead to a relatively large voltage gradient within the heart. This fits with the large changes in STT integral amplitudes, but would have led to a slight QT-interval prolongation. In Fig. 7B – besides a heterogeneous and small pressure-induced RT prolongation – AP morphology is changed at the end of repolarization.

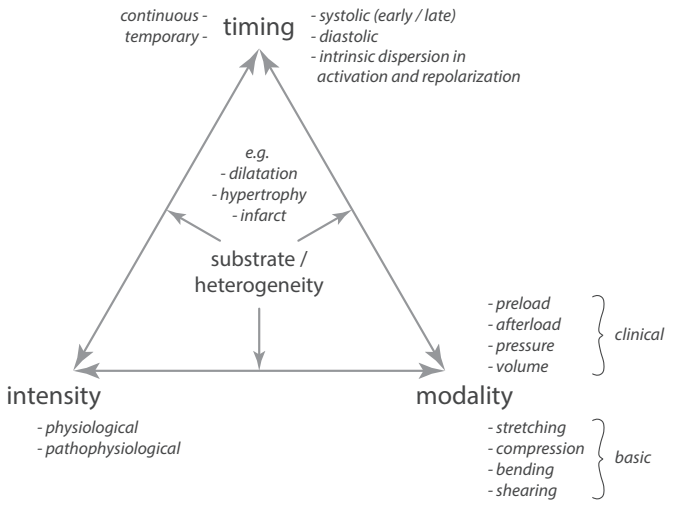

Fig. 6. MEC classification and interaction.
MEC triangle explaining the classification of MEC and interactions. The *timing* indicates the duration of the stretch pulse or the timing relative to the phase of action potential. The *intensity* refers to the extent of stretch applied and can be grossly divided in physiological and pathophysiological levels of stretch. The *modality* of stretch is multifaceted and can be divided according to either basic strain measures or to clinical strain measures. The *substrate* of the heart may influence each of the interactions and complicates the classification due to presence of heterogeneity in each of the three factors. Examples of heterogeneities in the three factors are repolarization dispersion for timing, interventricular pressure differences for intensity and fibrotic area for modality.

This will lead to larger changes in STT integral amplitudes and a large QT prolongation. Fig. 7C supposes an AP morphology with a slower repolarization phase at baseline. Small pressure-induced RT prolongations will lead in this case to a much smaller voltage gradient per time unit, but will finally sum up to similar STT integral amplitudes as in the Fig. 7A. Also, a rather small QT prolongation will be present. Thus, we reason that the increased LV pressure leads to a terminal AP morphology change involving only minor RT changes in our experiments (Figs. 1–4 and 7B). This is consistent with the AP prolongation resembling an afterdepolarization described by Franz et al. (Franz, 1996). We note that we sampled only the epicardium and therefore cannot exclude the possibility that endocardium repolarized later and may have contributed to the QT prolongation as well.

We also observed increased dispersion in repolarization in the entire heart (by 17 ± 9 ms, Table 2). This was mainly caused by an increased interventricular RT dispersion in 4 out of the 5 hearts. In these hearts the minimum RT was in the RV and the maximum RT was in the LV as described earlier (Meijborg et al., 2014). The increased dispersion of repolarization may also explain the increase in amplitude of the STT integrals (Zabel et al., 1995). The unchanged angle of the STT integral dipole vector implicates that the heterogeneity in RT remained in the same direction (i.e. left to right) corresponding to the interventricular dispersion which was already present at baseline, although to a smaller extent. The increased dispersion of repolarization, however, is in contrast with our recent study that demonstrated that (normal) pressure in a normal heart contributes to synchronization of the repolarization (Opthof et al., 2015). It is also in contrast with the study of James, that showed an inverse relation between QT dispersion and ventricular loading (James et al., 2002). The discrepancy may be explained by methodological differences related with the three factors mentioned before (Fig. 6). In the study of Opthof et al. diastolic and systolic pressures (0 and 0–100 mmHg, respectively) were within physiological ranges (intensity) and

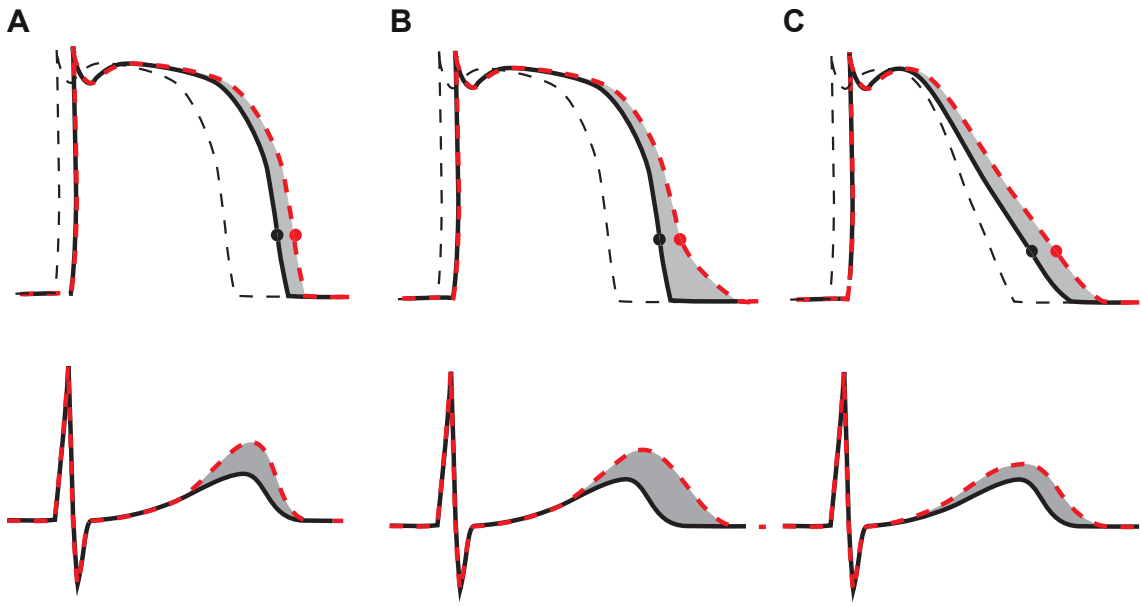

Fig. 7. Proposed hypotheses for STT-segment changes.
Illustrations of proposed hypotheses explaining STT-segment changes on the ECG caused by action potential (AP) changes. The *black lines* (*solid* and *striped*) show the baseline situation with short APs from the right ventricle (RV) and longer APs from the left ventricle (LV) resulting in a normal ECG. The *red striped lines* show the changes in AP in the LV and in the ECG. Dots at the descending AP limbs depict repolarization times (RTs). A) Small RT changes, resulting in a large T-wave amplitude with only slight QT prolongation. B) Small RT changes resulting in a large T-wave amplitude with large QT prolongation. C) Small RT changes resulting in a small T-wave amplitude with little QT prolongation.

only the systolic pressure was increased without changing the diastolic pressure and therefore inducing changes only during systole (timing). In addition, the timing of the moment of halfway peak pressure was shorter in our study (~110 ms vs 159 ms in earlier study). This could have been the result of different pacing conditions, because the heart rate (cycle length of 650 ms vs 450 ms in the earlier study) and pacing location (atrial vs ventricular pacing in the earlier study) have a large impact on the intrinsic dispersion in activation and repolarization and the timing with the contraction pulse. The absence of balloon inflation in the RV may explain the unaltered repolarization in the RV and the concomitant increase in interventricular dispersion of repolarization in the present study. This was possibly undetected in our earlier study (Opthof et al., 2015), because the RV was not sampled. Nevertheless, the LV intraventricular dispersion of RT was increased instead of reduced. Overall, this led to an increase in STT-segment amplitude, which cannot be reconciled with the inverse relation of the QT dispersion with the ventricular loading shown by James et al. 2002. However, the latter study was performed during in vivo and could have been influenced by autonomic modulation (Sedova et al., 2011). Despite the drawbacks described above, our model is more physiological than cellular or tissue models and the increased LV diastolic pressures causing increased repolarization heterogeneity may be of relevance for arrhythmogenesis in left-sided heart failure.

5.3. ECG and cardiac geometry

A second component, unrelated to MEC, that should be considered as well, is the change in cardiac geometry. Contraction of the heart results in movement (i.e. rotation, translation and deformation) of the electrical source with respect to the electrodes on the body surface. Some mathematical models have been developed to explore the effect of geometrical changes of the heart on the ECG. All models demonstrated that the implementation of motion in the heart lead to changes in the STT-segment and not so much in the QRS complex (Appleton et al., 2005; Jiang et al., 2009; Wei et al., 2006; Xia et al., 2006, 2005). The T-wave amplitude was lower in the dynamic heart compared to the static heart (Appleton et al., 2005; Keller et al., 2011; Wei et al., 2006; Xia et al., 2006, 2005). Smith and colleagues simulated the deformation effect and the MEC effect separately and demonstrated that deformation resulted in reduction of the T-wave amplitude, whereas MEC resulted in a leftward shift of the T-wave (Smith et al., 2003). These studies imply that changes in motion of the heart should also be incorporated in the effect on the ECG.

In addition, volume changes in the heart due to alteration in loading may also influence the ECG. In the present study, the balloon inflation itself caused a volume expansion of the heart, and a reduction of the distance between the ventricular walls and the electrodes on the bucket. This may have led to increased potential levels in the ECG (QRS and STT alike) and may therefore also have contributed directly to the increased amplitudes in QRS and STT integral maps. However, since repolarization was significantly prolonged, the expansion of the heart due to balloon inflation likely plays a minor role in STT-segment deviations. In addition, the absolute amplitude increase of the QRS integrals was smaller than that of the STT integrals.

6. Conclusion

Three factors (timing, intensity and modality of stretch) should be taken into account to analyse the effects of MEC on the heart and on the ECG. Deformation of the heart itself, should be considered as well, since it influences the amplitude of the STT-segment. We demonstrate that the STT-segments on the ECG are influenced by an increase in systolic and diastolic pressures. Because the electrocardiographic T-wave represents heterogeneity in repolarization, MEC may have influence on the inducibility of (re-entrant) arrhythmias.

Conflict of interest

None.

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Disclosures

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References

Appleton, B., Wei, Q., Crozier, S., Liu, F., Wilson, S., Xia, L., Liu, N., 2005. An electrical heart model incorporating real geometry and motion. Conf. Proc. IEEE Eng. Med. Biol. Soc. 1, 345–348. http://dx.doi.org/10.1109/IEMBS.2005.1616415.

Baumgarten, C.M., Clemo, H.F., 2003. Swelling-activated chloride channels in cardiac physiology and pathophysiology. Prog. Biophys. Mol. Biol. 82, 25–42. http://dx.doi.org/10.1016/S0079-6107(03)00003-8.

Benditt, D.G., Kriett, J.M., Tobler, H.G., Gornick, C.C., Detloff, B.L.S., Anderson, R.W., 1985. Electrophysiological effects of transient occlusion in intact canine heart aortic. Am. J. Physiol. 249, H1017–H1023.

Coronel, R., de Bakker, J.M.T., Wilms-Schopman, F.J.G., Opthof, T., Linnenbank, A.C., Belterman, C.N.W., 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. http://dx.doi.org/10.1016/j.hrthm.2006.05.027.

Coronel, R., Wilders, R., Verkerk, A.O., Wiegerinck, R.F., Benoist, D., Bernus, O., 2013. Electrophysiological changes in heart failure and their implications for arrhythmogenesis. Biochim. Biophys. Acta 1832, 2432–2441. http://dx.doi.org/10.1016/j.bbadis.2013.04.002.

Craelius, W., Chen, V., el-Sherif, N., 1988. Stretch activated ion channels in ventricular myocytes. Biosci. Rep. 8, 407–414.

Day, C.P., McComb, J.M., Campbell, R.W., 1990. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br. Heart J. 63, 342–344. http://dx.doi.org/10.1136/hrt.63.6.342.

Ford, L.E., Campbell, N.P., 1980. Effect of myocardial shortening velocity on duration of electrical and mechanical systole. S2T interval as measure of shortening rate. Br. Heart J. 44, 179–183.

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

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, 968–978. http://dx.doi.org/10.1161/01.CIR.86.3.968.

Guharay, F., Sachs, F., 1984. Stretch-activated single ion channel currents in tissue-cultured embryonic chick skeletal muscle. J. Physiol. 352, 685–701. http://dx.doi.org/10.1113/jphysiol.1984.sp015317.

Haemers, P., Sutherland, G., Cikes, M., Jakus, N., Holemans, P., Sipido, K.R., Willems, R., Claus, P., 2015. Further insights into blood pressure induced premature beats: transient depolarizations are associated with fast myocardial deformation upon pressure decline. Hear. Rhythm 12, 2305–2315. http://dx.doi.org/10.1016/j.hrthm.2015.06.037.

Han, J., Moe, G.K., 1964. Nonuniform recovery of excitability in ventricular muscle. Circ. Res. 14, 44–60.

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.

Isenberg, G., Kazanski, V., Kondratev, D., Fiora, M., Kiseleva, I., Kamkin, A., 2003. Differential effects of stretch and compression on membrane currents and [Na +] c in ventricular myocytes, 82, 43–56. http://dx.doi.org/10.1016/S0079-6107(03)00004-X.

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, 149–152.

Janse, M.J., Coronel, R., Wilms-Schopman, F.J.G., de Groot, J.R., 2003. Mechanical effects on arrhythmogenesis: from pipette to patient. Prog. Biophys. Mol. Biol. 82, 187–195. http://dx.doi.org/10.1016/S0079-6107(03)00015-4.

Jiang, M., Xia, L., Shou, G., Wei, Q., Liu, F., Crozier, S., 2009. Effect of cardiac motion on solution of the electrocardiography inverse problem. IEEE Trans. Biomed. Eng. 56, 923–931. http://dx.doi.org/10.1109/TBME.2008.2005967.

Kaufmann, R.L., Hennekes, R., Lab, M.J., 1971. Demonstration of an "Excitation-Contraction recoupling" mechanism in mammalian ventricular myocardium. Nat. New Biol. 230, 150–151.

Keller, D.U.J., Jarrousse, O., Fritz, T., Ley, S., Dossel, O., Seemann, G., 2011. Impact of physiological ventricular deformation on the morphology of the T-wave: a hybrid, static-dynamic approach. IEEE Trans. Biomed. Eng. 58, 2109–2119. http://dx.doi.org/10.1109/TBME.2011.2147785.

Kjekshus, J., 1990. Arrhythmias and mortality in congestive heart failure. Am. J. Cardiol. 65, 42I–48I.

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.

Kohl, P., Ravens, U., 2003. Cardiac mechano-electric feedback: past, present, and prospect. Prog. Biophys. Mol. Biol. 82, 3–9. http://dx.doi.org/10.1016/S0079-6107(03)00022-1.

Lab, M.J., 1982. Contraction-excitation feedback in myocardium. Physiological basis and clinical relevance. Circ. Res. 50, 757–766. http://dx.doi.org/10.1161/01.RES.50.6.757.

Lab, M.J., 1978. Mechanically dependent changes in action potentials recorded from the intact frog ventricle. Circ. Res. 42, 519–528. http://dx.doi.org/10.1161/01.RES.42.4.519.

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. http://dx.doi.org/10.1161/01.CIR.77.1.70.

Liang, Y., Kongstad, O., Luo, J., Liao, Q., Holm, M., Olsson, B., Yuan, S., 2005. QT dispersion failed to estimate the global dispersion of ventricular repolarization measured using monophasic action potential mapping technique in swine and patients. J. Electrocardiol. 38, 19–27. http://dx.doi.org/10.1016/j.jelectrocard.2004.09.012.

Meijborg, V.M.F., Conrath, C.E., Opthof, T., Belterman, C.N.W., De Bakker, J.M.T., Coronel, R., 2014. Electrocardiographic T wave and its relation with ventricular repolarization along major anatomical axes. Circ. Arrhythmia Electrophysiol. 7, 524–531.

Noble, D., Cohen, I., 1978. The interpretation of the T wave of the electrocardiogram. Cardiovasc. Res. 12, 13–27.

Opthof, T., Coronel, R., Wilms-Schopman, F.J.G., Plotnikov, A.N., Shlapakova, I.N., Danilo, P., Rosen, M.R., Janse, M.J., 2007. Dispersion of repolarization in canine ventricle and the electrocardiographic T wave: Tp-e interval does not reflect transmural dispersion. Hear. Rhythm 4, 341–348. http://dx.doi.org/10.1016/j.hrthm.2006.11.022.

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. http://dx.doi.org/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, 235. http://dx.doi.org/10.3389/fphys.2012.00235.

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. http://dx.doi.org/10.1016/j.pbiomolbio.2014.06.007.

Sedova, K. a., Goshka, S.L., Vityazev, V. a., Shmakov, D.N., Azarov, J.E., 2011. Load-induced changes in ventricular repolarization: evidence of autonomic modulation. Can. J. Physiol. Pharmacol. 89, 935–944. http://dx.doi.org/10.1139/y11-098.

Shub, C., 1989. Heart failure and abnormal ventricular function. Pathophysiology and clinical correlation (Part 1). Chest 96, 636–640. http://dx.doi.org/10.1378/chest.94.4.845.

Smith, N.P., Buist, M.L., Pullan, A.J., 2003. Altered T wave dynamics in a contracting cardiac model. J. Cardiovasc. Electrophysiol. 14, S203–S209. http://dx.doi.org/10.1046/j.1540.8167.90312.x.

Taggart, P., 1996. Mechano-electric feedback in the human heart. Cardiovasc. Res. 32, 38–43.

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, 221–229.

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–H823.

Taggart, P., Sutton, P.M., 1999. Cardiac mechano-electric feedback in man: clinical relevance. Prog. Biophys. Mol. Biol. 71, 139–154.

Tomaselli, G.F., Zipes, D.P., 2004. What causes sudden death in heart failure? Circ. Res. 95, 754–763. http://dx.doi.org/10.1161/01.RES.0000145047.14691.db.

Wei, Q., Liu, F., Appleton, B., Xia, L., Liu, N., Wilson, S., Riley, R., Strugnel, W., Slaughter, R., Denman, R., Crozier, S., 2006. Effect of cardiac motion on body surface electrocardiographic potentials: an MRI-based simulation study. Phys. Med. Biol. 51, 3405–3418. http://dx.doi.org/10.1088/0031-9155/51/14/009.

Xia, L., Huo, M., Wei, Q., Liu, F., Crozier, S., 2006. Electrodynamic heart model construction and ECG simulation. Methods Inf. Med. 45, 564–573.

Xia, L., Huo, M., Wei, Q., Liu, F., Crozier, S., 2005. Analysis of cardiac ventricular wall motion based on a three-dimensional electromechanical biventricular model. Phys. Med. Biol. 50, 1901–1917. http://dx.doi.org/10.1088/0031-9155/50/8/018.

Zabel, M., Koller, B.S., Sachs, F., Franz, M.R., 1996. 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.

Zabel, M., Portnoy, S., Franz, M.R., 1995. Electrocardiographic indexes of dispersion of ventricular repolarization: an isolated heart validation study. J. Am. Coll. Cardiol. 25, 746–752. http://dx.doi.org/10.1016/0735-1097(94)00446-W.