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REVIEWS

# The importance of non-uniformities in mechano-electric coupling for ventricular arrhythmias

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**Abstract** Cardiac mechanical and electrical activities are tightly linked through an intra-cardiac regulatory loop (mechano-electric coupling). This connection is essential for normal heart function and auto-regulation. In diseases associated with altered myocardial mechanical properties or function, however, feedback from the mechanical environment to the origin and spread of excitation can result in deadly cardiac arrhythmias. Ventricular tachyarrhythmias, especially, are encountered in cardiac diseases associated with volume and pressure overload or changes in tissue mechanics. Little is known about the influence of changes in mechano-electric coupling on cardiac rhythm in these settings or the potential therapeutic benefit of its manipulation. Improved understanding may be central to explaining the origin of arrhythmias that occur with these pathologies and to the development of novel mechanics-based therapies. The present review explores the potential role of mechano-electric coupling in ventricular arrhythmogenesis, with a focus on the importance of non-uniformity in mechanical function for the induction and sustenance of ventricular tachyarrhythmias.

**Keywords** Arrhythmias · Cardiac electrophysiology · Cardiac mechanics · Heterogeneity · Mechano-electric coupling · Ventricle

## 1 Introduction

Cardiac mechanics and electrophysiology are exquisitely linked (Fig. 1). This link involves well established feed-forward connections between electrical excitation and mechanical contraction (excitation–contraction coupling, ECC) [1], as well as less appreciated feedback from the mechanical environment to the origin and spread of excitation (mechano-electric feedback, MEF) [2]. The result is an intra-cardiac mechano-electric regulatory loop (mechano-electric coupling, MEC), which is essential for normal function and (auto-)regulation of the heart (extensively examined in a book dedicated to the subject [3]). MEC can be observed at all levels of cardiac structural and functional integration, from the (sub-)cellular and tissue level, to the whole organ and in patients. Consequently, disease-related alterations in myocardial mechanical properties or function may contribute to electrophysiological changes responsible for deadly arrhythmias. Ventricular tachyarrhythmias (VTs), with an accompanying increase in morbidity and mortality, are frequently encountered in pathologies associated with volume and pressure overload or changes in tissue mechanics, such as valve disease, cardiomyopathy, heart failure, hypertrophy, ischemia, and infarction [4, 5]. There is also growing evidence that manipulation of the ventricular mechanical environment can have beneficial effects [6–10]. This suggests that it may be possible to develop novel treatments for preventing life-threatening ventricular arrhythmias in cases where pathological changes in MEC are occurring, for instance in the first hours after a heart attack or in the progression of heart failure. However, little is known about the influence of MEC on cardiac rhythm in these settings. If new therapies based on its manipulation are to be realized, a better understanding of the role that mechanically induced changes in ventricular electrophysiology play in arrhythmogenesis is needed. The present review explores the potential role of MEC in ventricular arrhythmias, with a focus on the importance of non-uniformity in mechanical function for the induction and sustenance of VTs.

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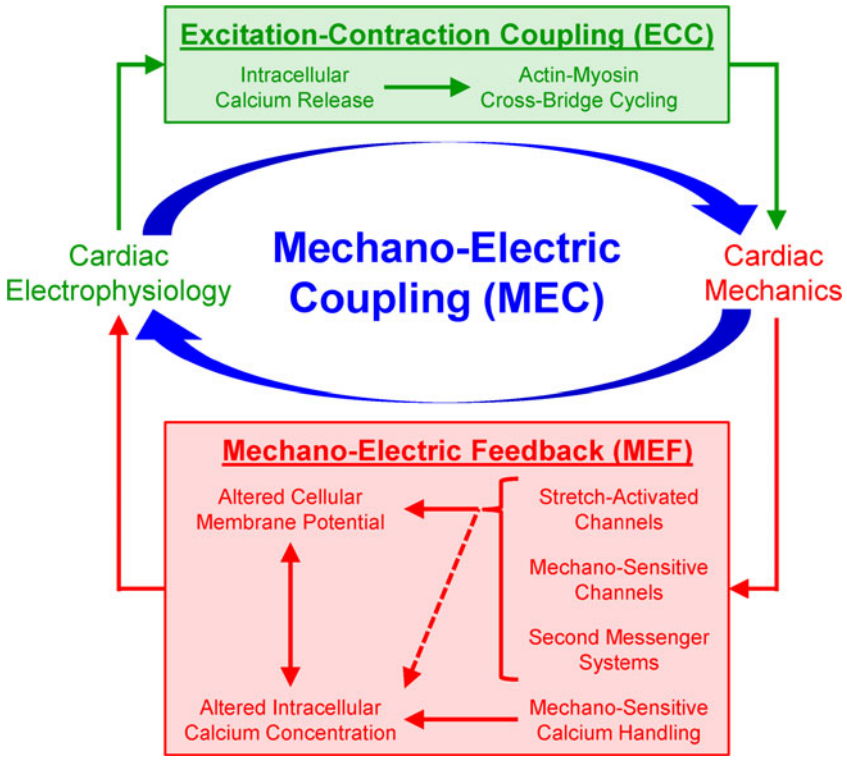



**Fig. 1** Schematic illustration of the "mechano-electric coupling" (MEC) concept, linking cardiac mechanics and electrophysiology. The feed-forward arm of this intra-cardiac regulatory loop is the connection between electrical excitation and mechanical contraction, involving intracellular calcium release and actin-myosin cross-bridge cycling, a process known as "excitation–contraction coupling" (ECC). Feedback occurs as myocardial deformation results in altered cell membrane potential and intracellular calcium concentration *via* multiple inter-dependent mechano-sensitive mechanisms, which in turn affect the origin and spread of excitation, a phenomenon known as "mechano-electric feedback" (MEF)

## 2 Evidence for a role of mechano-electric coupling in ventricular tachyarrhythmias

The current lack of understanding about the importance of mechanical factors in the genesis of ventricular arrhythmias is in large part due to the difficulty of identifying clear causation in the chronic setting. Changes in MEC occur at the same time as remodeling of tissue and cell structure and function, changes in ion channel expression and dynamics, and alterations of metabolic and autonomic state. As such, considering acute effects, even in the chronic setting, can help to elucidate the importance of mechanical stimuli in the induction and maintenance of VTs. One of the most striking examples of this is the result of temporary *removal* of ventricular volume overload in patients suffering from chronic ventricular tachycardia. The Valsalva maneuver, which results in a reduction of ventricular volume due to blood redistribution by a change in the thoracic-abdominal pressure gradient, is able to terminate VTs, which return upon the restoration of load [8, 11]. This is associated with changes in repolarization and differs in patients with and without wall motion abnormalities [12]. VTs can also be terminated by repeated forceful coughs through a similar mechanism [10]. Importantly, the termination of VTs by unloading continues to occur after surgical denervation of the heart (in transplant recipients) [9, 12], suggesting that underlying mechanisms are intrinsic to the myocardium.

More commonly, the effects of acute *application* of mechanical load are investigated, often in the healthy heart [13]. In one of the classic illustrations of MEC, a transient increase in intraventricular volume in isolated hearts during diastole causes membrane depolarization [14], which, if sufficiently large, triggers ectopy [15]. When volume is increased instead during early repolarization (a period characterized by an enhanced dispersion of repolarization), short runs of ventricular tachycardia [16, 17] or ventricular fibrillation [18, 19] can be induced. Increasing intraventricular load *in situ* also results in VTs [14, 20, 21], which may in part be a consequence of a load-related decrease in the threshold for VTs induction [22–24]. Likewise, in patients, VTs occur with increases in intraventricular volume during balloon valvuloplasty [25], and in heart failure, there is an association between average daily median pulmonary artery pressure and the risk of VTs [26]. Mechanically induced VTs are also commonly caused by central venous and pulmonary artery catheters [27] (with incidences of up to 40 % in some cases [28]), by contact of intracardiac catheters and electrodes with the myocardium (Fig. 2) [29–31], during chest compressions after electrical defibrillation [32], or by non-traumatic impacts to the precordium (in the setting of *Commotio cordis*) [33].

Thus, mechanical stimulation of ventricular myocardium can result in the induction of VTs in healthy and diseased hearts and may play a sustaining role in chronic pathological states. The mechanisms by which mechanical stimulation leads to ventricular arrhythmias, however, remain unclear.

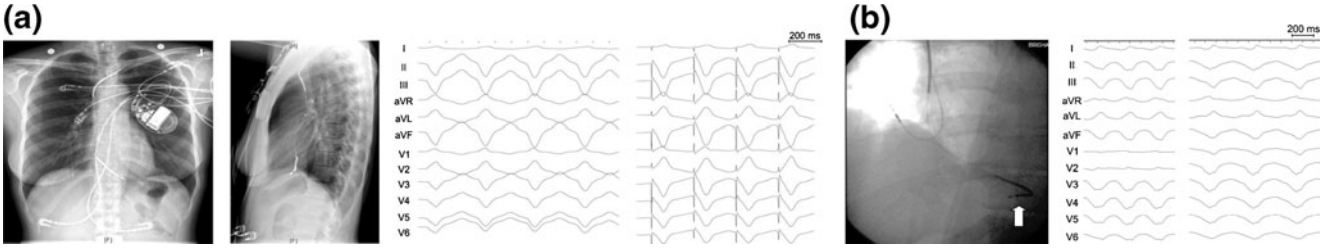



**Fig. 2** **a** Posterior–anterior (*first panel*) and lateral (*second panel*) chest radiographs showing an implantable cardioverter-defibrillator (ICD) lead with appropriate positioning, but limited redundancy. In this patient, clinical ventricular tachycardia occurred with exercise or isoproterenol testing as shown on the ECG (*third panel*), which was nearly identical to the right bundle branch block superior axis configuration produced by pacing at the ICD lead tip (*fourth panel*). **b** Anterior fluoroscopic image showing distal ICD lead angulation, indicated by the arrow (*first panel*). In this patient, clinical ventricular tachycardia was present (*second panel*), which was nearly identical to the left bundle branch block superior axis configuration produced by pacing next to the ICD lead (*third panel*). In both cases, arrhythmias ceased after lead extraction and patients remained arrhythmia free without antiarrhythmic drug therapy, suggesting a mechanical effect. Adapted from [30]

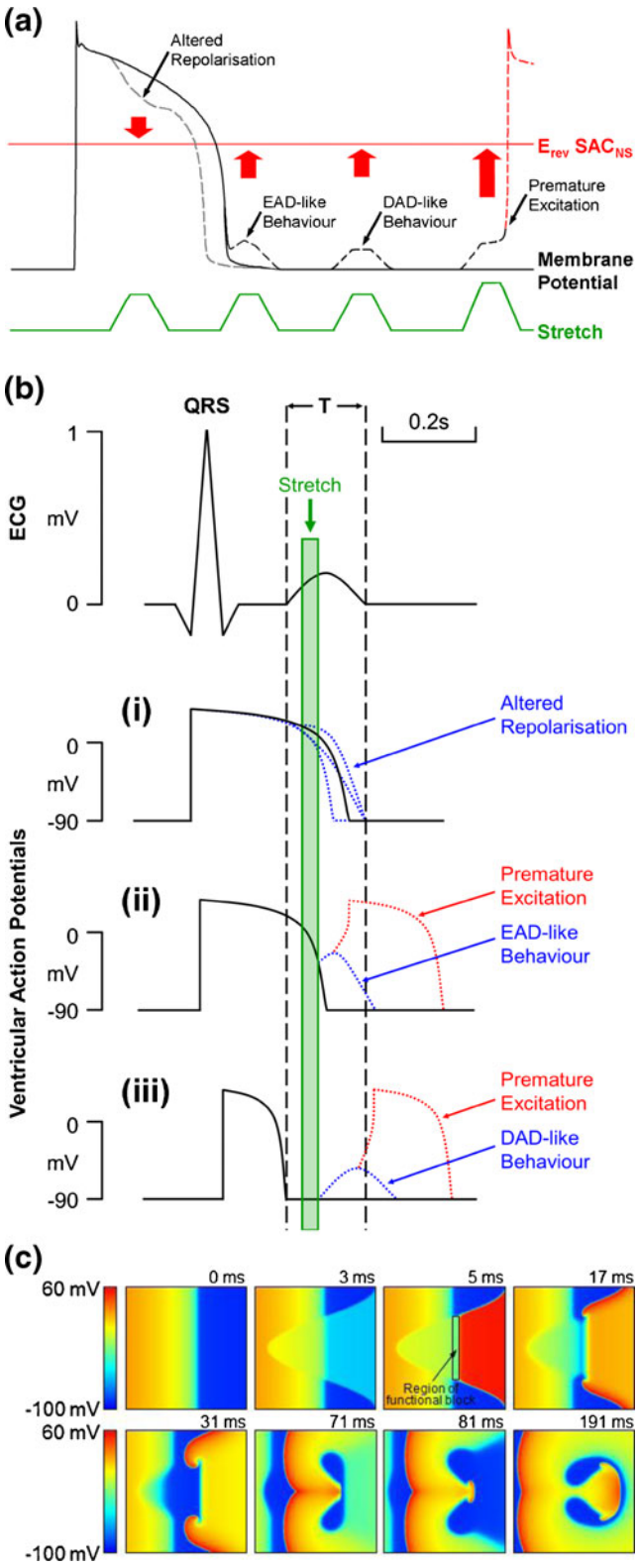
## 3 Spatio-temporal dependence of mechanical stimulation for ventricular re-entry

Conceptually, VTs are thought to arise as a result of the combined action of a *trigger* and a *substrate for re-entry* [34]. In disease, both triggers and substrates for VTs can be the result, at least in part, of electrophysiological responses to mechanical stimuli [35–37]. Results from cell, tissue, and whole heart experiments, combined with results from computational studies, have helped to suggest a mechanism by which ventricular mechanical stimulation may result in the induction of re-entrant electrical activity [38–40]. As a trigger, ectopy requires cellular depolarization. With stretch, this can be explained by activation of a mechano-sensitive ion current in ventricular myocytes with a reversal potential around halfway between peak action potential and resting potential levels. This current is thought to be carried by cation non-selective stretch-activated channels ($SAC_{NS}$) [41], which are involved in triggering excitation of myocardial cells [42], tissue [43], and the whole heart [15].

Compared to mechanical triggering, the source and nature of the substrate for mechanically induced re-entry is less clear. In ventricular myocytes whose membrane potential is above the reversal potential of $SAC_{NS}$ (during early repolarization), stretch tends to cause cellular *repolarization* and action potential shortening (Fig. 3a) [44]. As the cell repolarizes further and passes the reversal potential of $SAC_{NS}$, stretch will again cause *depolarization*, prolonging the action potential [45], and potentially giving rise to early and delayed after-depolarization-like behavior (Fig. 4a).

It is important to note, however, that even in healthy hearts repolarization at the whole ventricle level is associated with significant spatial non-uniformity in membrane potential and refractoriness. While the ventricular activation wave-front is steep and fast (reflected by the narrow QRS complex of the ECG), repolarization is a more graded process (revealed by the broader and lower ECG T wave; Fig. 3b). This means that mechanical stimulation during ventricular repolarization will affect myocytes in different phases of the action potential in different regions of the ventricle (as opposed to during activation, when comparatively little room for regional differences exists). Consequently, some cells in the ventricles will be excited, providing an arrhythmic trigger, while other cells will have their repolarization altered [46]. The result will be an increase in dispersion of ventricular electrophysiology that can result in regions of slowed conduction and functional block, furnishing a substrate for re-entry (Fig. 3b) [47]. In patients, it is in fact the degree of changes in the spatial heterogeneity of repolarization (rather than simply the amplitude of changes in repolarization) that is important for arrhythmogenesis [48].

The quantitative *plausibility* of mechanisms by which mechanical stimulation can lead to electrical re-entry has been explored with the aid of computational modeling [49, 50]. Two- [51] and three-dimensional [52] models of ventricular tissue have demonstrated that mechanically induced sustained arrhythmias may occur *only* when a mechanical stimulus affects myocardial tissue such that it: (1) includes tissue that has regained excitability (allowing ectopy to occur), (2) overlaps with the trailing wave of repolarization from the preceding cardiac cycle (where the intersection of new activation and refractory tissue gives rise to an area of functional block of conduction), and (3) extends into tissue at membrane potential levels above the reversal potential of $SAC_{NS}$ (so that regional action potential shortening generates an additional arrhythmia-sustaining substrate; Fig. 3c). This computational prediction is currently being experimentally investigated by examining the characteristics of mechanically induced ectopy in the whole heart and its potential for induction of sustained arrhythmias. By the application of controlled, non-traumatic, local mechanical stimuli in isolated, Langendorff-perfused rabbit hearts, while monitoring membrane potential by fluorescent optical mapping, it has recently been shown that sufficiently large local deformation in diastole results in focal excitation (Fig. 4a), which is at least partly dependent on $SAC_{NS}$ activation [53]. Upon reduction of the delay for mechanical stimulation relative to the QRS complex, ectopy-




◀ **Fig. 3** **a** Effects of stretch (*green line*) on the membrane potential of ventricular myocytes (*solid black line*). Depending on stretch timing, the action potential may be shortened (*gray dashed line*) or the cell may depolarize (*black dashed line*), resulting in early (EAD) or delayed (DAD) after-depolarization-like behavior, and with sufficient stretch, excitation (*red dashed line*). The *solid red line* shows the cation non-selective stretch-activated channel ($SAC_{NS}$) reversal potential ($E_{rev}$), towards which membrane potential is drawn (adapted from [39]). **b** Effects of mechanical stimulation during the ECG T wave (*green bar*) in the whole heart. Regionally varying response depends on the local phase of the action potential: *(i)* altered action potential duration in slightly repolarized regions and *(ii)* EAD or *(iii)* DAD-like behavior in more repolarized regions, potentially triggering premature excitation (adapted from [46]). **c** Computer simulation of mechanically induced sustained re-entry in ventricular tissue, which depends on the spatio-temporal relation of the mechanical stimulus and underlying electrical activity, such that ectopy is triggered in regions that have regained excitability, overlap with the trailing wave of repolarization generates a region of functional block, and action potential shortening in slightly repolarized regions contributes to an arrhythmia-sustaining substrate (adapted from [51])

induction continues until stimulation coincides with the stage of repolarization when mechanically affected tissue overlaps the repolarization wave [54]. This is the only setting in which induction of re-entry and fibrillation is observed.

Thus, by fostering both a trigger and substrate for re-entrant excitation, mechanical stimulation can result in the genesis of VTs, with its *spatio-temporal* relation to underlying electrophysiology being of critical importance.

## 4 Non-uniformity of mechano-electric coupling in mechanically induced ventricular tachyarrhythmias

Due to the dependence of electrophysiological outcomes on the spatio-temporal nature of mechanical stimulation, an important consideration for the mechanical induction of arrhythmias is potential non-uniformity of MEC effects. Myocardial stiffness varies throughout the ventricles due to anisotropy of structure, active contraction, and passive viscoelasticity. Therefore, even *global* mechanical stimulation, such as a change in intraventricular volume, can result in *spatially heterogeneous* effects. This is apparent from experimental evidence showing that an increase in intraventricular volume results in non-uniform stretch, which is associated with heterogeneity of depolarization [19, 20]. As a consequence, with increased intraventricular volume, excitation generally originates from the region of largest stretch, typically the ventricular free wall (a region of relatively low stiffness; Fig. 4b) [15, 19, 20]. This occurs at the same time as an increase in the dispersion of repolarization and refractoriness [18, 20, 22, 55, 56]. Many cardiac diseases involve heterogeneous changes in ventricular stiffness and mechanical function [57], further increasing stretch non-uniformity. This non-uniformity is associated with a high susceptibility to VTs and is one of the largest predictors of sudden cardiac death [4]. The apparent increase in the importance of MEC in these cases, however, is difficult to assess, as the consequences of non-uniform mechanical

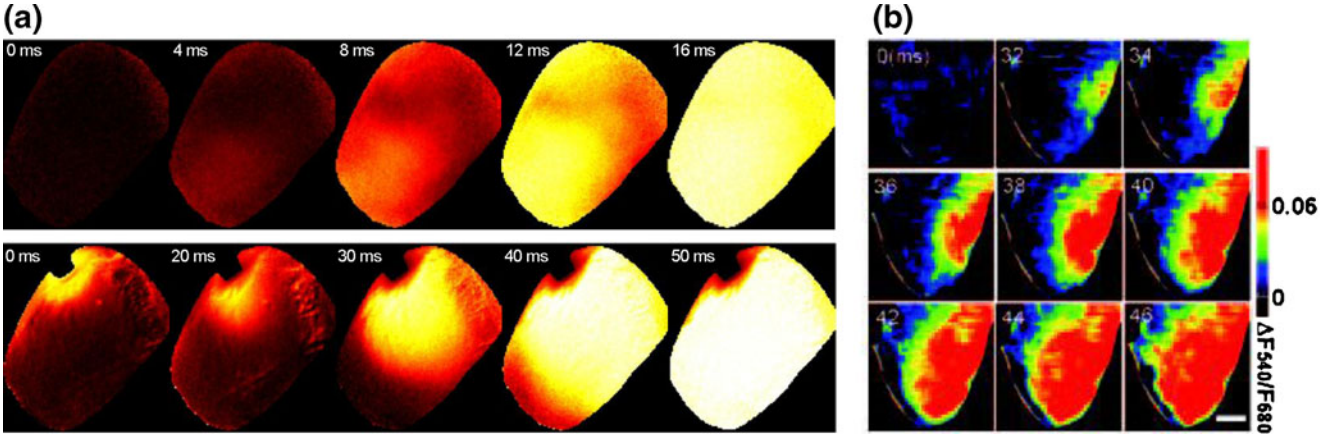



**Fig. 4** Voltage optical mapping in isolated hearts showing: **a** sinus node-induced ventricular activation (occurring in the apex to base direction, with sites of epicardial breakthrough; *top panel*) and local mechanically induced ventricular activation (occurring as a wave of excitation originating from the site of mechanical stimulation; *bottom panel* [unpublished data]) and **b** focal ventricular activation originating from the ventricular free wall due to an increase in intraventricular volume (adapted from [19])

activity are complex. "Independent," yet "mechanically linked," muscle segments interact in a highly dynamic manner, affecting each other's electromechanical activity based on the mode of contraction (isometric or isotonic), the spatial arrangement of muscle elements (in-series or in-parallel), the relative timing of mechanical and electrical events, and the electrical activation sequence [58, 59].

For instance, in acute regional ischemia, focal excitation largely occurs at the ischemic border (Fig. 5a) [60], an area of particularly high stretch due to systolic segment lengthening [61–65], whose magnitude relates to the onset of ventricular fibrillation [66]. Similarly, the degree of end-diastolic stretch of an ischemic region is a strong predictor of ventricular fibrillation probability [67]. Importantly, the incidence of arrhythmias during ischemia is potentiated by an enhanced strength of contraction after an extended diastolic pause and is greater in hearts working against an internal load than in unloaded ventricles (Fig. 5a) [60], as well as in ventricles with increased intraventricular volume [68]. In patients with ischemia, there is a strong correlation between the presence of regional wall motion abnormalities and the occurrence of arrhythmias [69, 70]. Furthermore, in 70 % of resuscitated survivors of out-of-hospital ventricular fibrillation with signs of ischemia by ECG, the anterior wall is involved, an area of greater excursion than the inferior wall during ischemia [35]. These data suggest a critical contribution of non-uniform MEC to the induction of arrhythmias during ischemia. Ischemia also affects MEC independent of changes in mechanics [71], through activation of additional mechano-sensitive mechanisms (such as the ATP-inactivated potassium [72] or volume-activated chloride [73] current) or by sympathetic stimulation [74], effects that have the potential to increase or decrease MEC-related responses.

In chronically infarcted hearts, on the other hand, increased intraventricular volume results in the initiation of VTs from the site of the largest change in repolarization [55], an effect that is abolished by block of $SAC_{NS}$ [75]. As such, in patients with acute myocardial infarction, afterload reduction abolishes severe arrhythmias [76, 77]. Interestingly, however, while infarct-related non-uniformity of ventricular contraction is associated with an increased dispersion of repolarization in humans, repolarization heterogeneity appears to occur primarily in the *normally contracting* regions of hearts with even moderate wall motion abnormalities, independent of the presence of infarction [78]. An important aspect of post-infarct scars to consider in the context of MEC is mechano-sensitivity of cardiac fibroblasts and their heterotypic coupling to ventricular myocytes [79]. Beyond the idea that connective tissue acts solely as an arrhythmogenic obstacle to electrical conduction [80], it is becoming clear that fibroblasts form electrotonic connections to myocytes that can act as current sinks, locally affecting myocyte excitability, repolarization, and conduction [81, 82], or serve as short- and long-range conductors between structurally separate myocyte groups [83, 84]. This heterotypic interaction, which is enhanced after myocardial infarction [85], may account for electrical wave propagation into transmural scars [86] (in which calcium transients, a signature activity of cardiac myocytes, are absent [87]). Thus, as fibroblasts possess $SAC_{NS}$ [88] and stretch results in their depolarization [89], they may be significantly involved in mechanically induced electrophysiological changes in infarcted hearts [90].

Some "electrical" diseases not thought to primarily involve mechanical dysfunction may also include important, yet underappreciated, contributions of non-uniform MEC (making them perhaps more appropriately thought of as "electro-mechanical" diseases). An excellent example is long QT syndrome, which is characterized by spatially heterogeneous prolongation of repolarization, leading to increased dispersion of action potential duration, QT

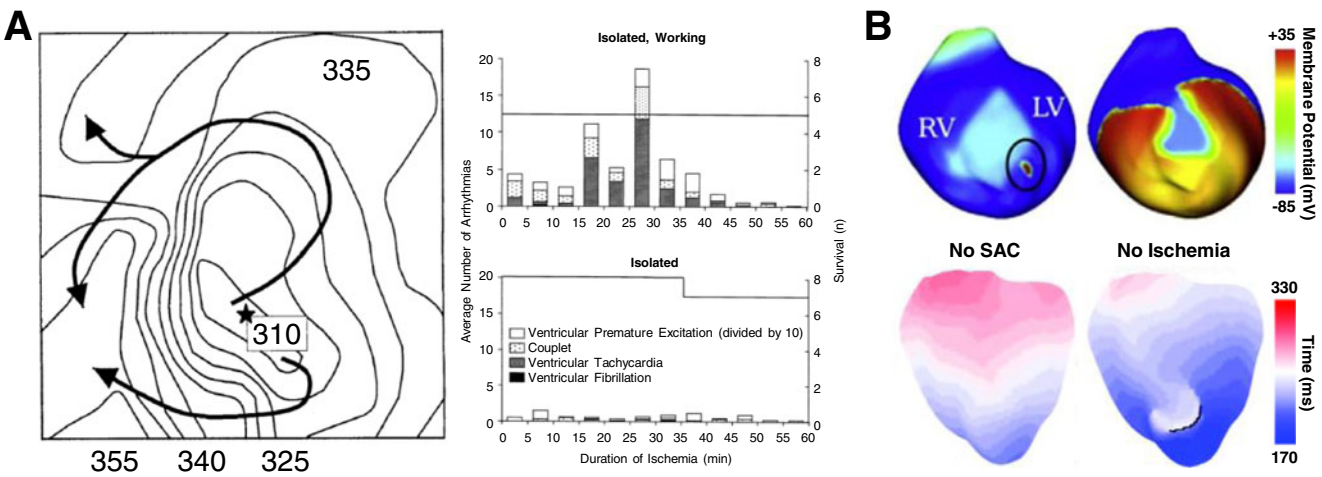



**Fig. 5** **a** Activation map of ventricular ectopy originating at the ischemic border during acute regional ischemia (*left*) and plots showing greater frequency of arrhythmias in working *versus* unloaded isolated hearts (*right*) (adapted from [60]). **b** Computational simulation of mechanically induced ventricular ectopy (*black circle*) and re-entry during acute regional ischemia (*top*) and simulated activation patterns without stretch-activated channels (SAC) or ischemic electrophysiological changes (*bottom*) (adapted from [104])

prolongation, polymorphic ventricular tachycardia, and sudden cardiac death [91]. In both transgenic and pharmacological models of long QT syndrome, there is a spatial correlation between regional action potential duration and diastolic dysfunction [92]. This link between regional heterogeneity in electrophysiology and mechanics may, *via* MEC mechanisms, work in both directions, such that changes in mechanical function feedback on electrical activity, contributing to the associated arrhythmias [93]. This possibility is supported by experimental work showing that, in drug-induced long QT syndrome, after-contractions of increasing amplitude in the ventricular endocardium precede epicardial after-depolarizations (presumably due to stretch of epicardial tissue [94]), which eventually reach the threshold for ventricular excitation, triggering *torsades de pointes* (Fig. 6a) [95].

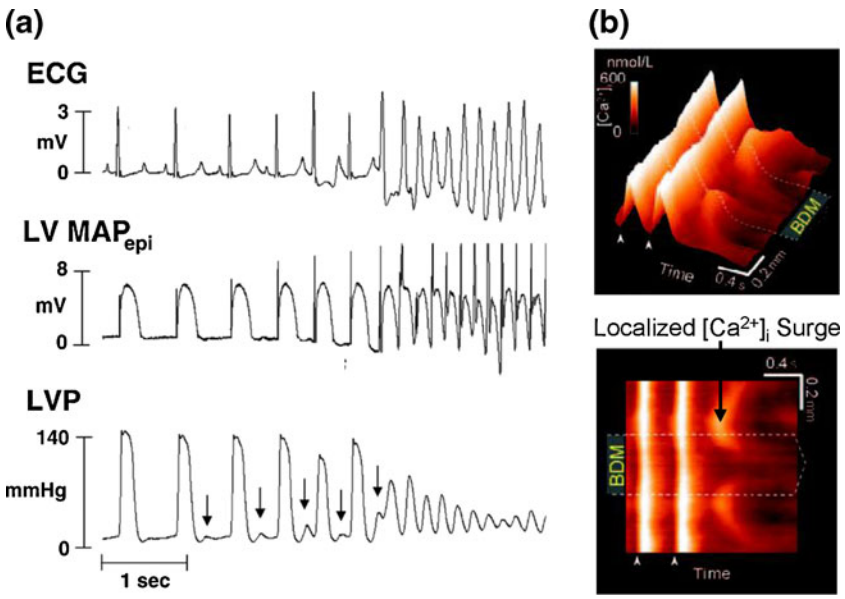



**Fig. 6** **a** After-contractions in the left ventricular (LV) endocardium of increasing amplitude (shown by *arrows* at the bottom trace of LV pressure, LVP) preceding epicardial after-depolarizations (middle trace of LV epicardial monophasic action potentials, MAP$_{epi}$), which eventually reach the threshold for ventricular excitation, triggering *torsades de pointes* (upper ECG trace) in a pharmacological model of long QT syndrome (adapted from [95]). (**b**) Three- (*top*) and two-dimensional (*bottom*) spatio-temporal representations of intracellular calcium concentration ([Ca$^{2+}$]$_i$) showing electrically stimulated [Ca$^{2+}$]$_i$ transients (*white arrows*), followed by a surge in [Ca$^{2+}$]$_i$ localized at the border between normal and weakened (by local perfusion with 2,3-butanedione monoxime, BDM) ventricular trabecular tissue, triggering a propagating [Ca$^{2+}$]$_i$ wave (adapted from [117])

Non-uniform stretch may also be important for sustaining established VTs. Stretch accelerates activation and increases VTs complexity (by producing more areas of transmural excitation breakthrough and conduction block) in a localized manner [96]. These effects are attenuated by block of $SAC_{NS}$ with streptomycin [97], by block of the sarcolemmal sodium-calcium exchanger with KB-R7943 [98], the β-blocker propranolol [98], and the mechanical uncouplers blebbistatin and 2,3-butanedione monoxime [99]. Of note, while pharmacological agents have thus far been used as an experimental tool to explore the role and mechanisms of MEC in electrophysiological stretch responses, there may be potential for their use to prevent or treat ventricular arrhythmias related to mechanical changes in the heart. The most promising agent currently is a relatively small peptide found in the venom of the *Grammostola spatulata* spider (*G.* mechanotoxin-4, GsMTx-4) [100]. At concentrations of 200 nm, GsMTx-4 suppresses stretch-induced focal excitation in the whole heart [53], as well as the incidence and duration of atrial fibrillation with elevated filling pressures [101], while not affecting action potentials of isolated myocytes at 20 times the concentration [101].

While the specific role of non-uniform mechanical activity in the induction and sustenance of VTs is difficult to assess experimentally, computational modeling has been helpful in elucidating its importance [102, 103]. Anatomically detailed, three-dimensional, electromechanical models have been used to support the concept that MEC plays an important role in arrhythmogenesis during acute regional ischemia [104]. Simulations have demonstrated that mechanically induced depolarization at the ischemic border zone *via* activation of $SAC_{NS}$ induces ectopy and causes conduction slowing and block, resulting in re-entry and VTs (Fig. 5b). Importantly, when $SAC_{NS}$ are omitted from the model, the diastolic depolarization, which accounts for this behavior, is absent. On the other hand, when ischemia-induced electrophysiological changes are omitted, ectopy and conduction slowing/block do not result in re-entry, suggesting that the combination of MEC and ischemic effects is necessary for the induction of VTs (Fig. 5b). Computational investigations have also supported the idea that MEC is involved in altering the complexity of sustained re-entrant electrical activity [105, 106].

The discussion thus far has focused mainly on the involvement of $SAC_{NS}$ in MEC responses, which can account for most acute mechanically induced changes in ventricular myocyte electrophysiology. Additional factors, however, may make important contributions to MEC in the ventricles, such as mechano-sensitivity of other sarcolemmal ion channels (for instance voltage gated sodium, calcium, or potassium channels), interaction with mechano-sensitive non-cardiomyocytes (such as Purkinje, endothelial, or smooth muscle cells, cardiac fibroblasts, or intracardiac neurons), or effects on a host of second messenger systems (all of which are explored in dedicated chapters in [3]).

The most relevant for the induction of VTs, however, is stretch-related changes in intracellular calcium handling. Calcium cycling in ventricular myocytes is directly affected by stretch in ways that may contribute to both the trigger and arrhythmic substrate needed for VTs induction [107–110]. Stretch causes an acute and transient increase in the spontaneous release of calcium from the sarcoplasmic reticulum (known as "calcium sparks") in ventricular myocytes by increasing ryanodine receptor open probability [111–113]. At the same time, intracellular calcium concentration is affected by a length-dependent change in the affinity of troponin-C for calcium, such that, with stretch, more calcium is in the bound state [114, 115]. This contributes to the Frank–Starling response of the heart and is thought to act as an equalizer of cell contractility, allowing individual cardiomyocytes to operate in mechanical balance with their neighbors. However, in the case of non-uniform mechanical activity, the increased affinity of troponin-C for calcium with stretch can give rise to arrhythmogenic calcium waves [116]. In stretched ventricular muscle, the dissociation of calcium from troponin-C during late twitch relaxation and rapid shortening causes a surge in intracellular calcium [117]. In this period, ryanodine receptors have sufficiently recovered to allow additional calcium-induced calcium release from the sarcoplasmic reticulum [118]. The locally increased intracellular calcium diffuses through the cell, triggering release of calcium in adjacent sarcomeres, and a propagating calcium wave (Fig. 6b). Cellular excitation may then ensue by depolarization *via* electrogenic calcium removal through the sarcolemmal sodium-calcium exchanger [119]. It is important to note that it is the *relaxation* of stretched muscle, rather than the stretch *per se*, that causes this calcium-mediated arrhythmic trigger, reinforced by the observation that calcium release is enhanced by increasing the rate of relaxation [120] and is independent of the involvement of $SAC_{NS}$ [121].

Thus, it appears that non-uniform stretch, whether applied regionally or resulting from heterogeneous translation of global mechanical perturbations, may contribute to ectopy and increased dispersion of repolarization and refractoriness. This may occur by alteration of trans-sarcolemmal ion balance or intracellular calcium handling and plays an important role in the initiation and sustenance of re-entrant ventricular arrhythmias.

## 5 Conclusion

The relative contribution of disease-related changes in MEC to changes in cardiac rhythm is unknown. A better understanding of their individual importance may be central to understanding arrhythmias seen in pathologies associated with changes in ventricular mechanical properties or function.

It is clear that acute mechanical stimulation of the ventricles can result in VTs, both by generating the necessary trigger and by contributing to arrhythmia-sustaining mechanisms. This most likely occurs through non-uniform stretch-induced changes in membrane potential by effects on trans-sarcolemmal currents and intracellular calcium cycling. However, in pathophysiological settings with altered mechanics, there exist concomitant changes in other arrhythmogenic factors, such as the electrophysiological background, autonomic tone, and tissue composition, that make it difficult, if not impossible, to assess the specific importance of MEC effects. Some evidence, suggesting that chronic non-uniform ventricular mechanical activity may have important long-term electrophysiological implications, does exist. For instance, mechanical dyssynchrony results in abnormal conduction and repolarization in late-activated regions [122, 123]. On the other hand, the combination of chronic improvements in mechanical uniformity along with ventricular unloading by biventricular pacing or left ventricular assist device therapy is associated with a reduction the frequency of ectopy and VTs [6, 7], as well as a decrease in the incidence of sudden cardiac death [124]. This reinforces the need for studies exploring the *individual contribution* of non-uniform MEC to arrhythmogenesis. Initial computational and *in vitro* studies have suggested a specific role for heterogeneous mechanical function in the induction of VTs, but further experimental validation is needed in whole heart and *in vivo* preparations. With the continuous development of novel imaging approaches, combined with advanced experimental and computational techniques, it is hoped that a link can be made between *global* descriptors of cardiac MEC activity (*e.g*., intraventricular volume/pressure and ECG) and *regional* behavior (*e.g*., high-resolution, spatially resolved mechanical and electrical activity). This is an essential step towards improving our understanding of the importance of MEC to cardiac rhythm. Ultimately, a better appreciation of the contribution of MEC effects in cardiac arrhythmogenesis may lead to improved devise- (focused around global or locally targeted alterations of ventricular load) or pharmacologically based therapies (potentially with the use of GsMTx-4 or other yet-to-be-identified agents) for the treatment and prevention of deadly ventricular arrhythmias.

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