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STATE OF THE ART REVIEW
Arrhythmias

Electromechanical reciprocity and arrhythmogenesis in long-QT syndrome and beyond

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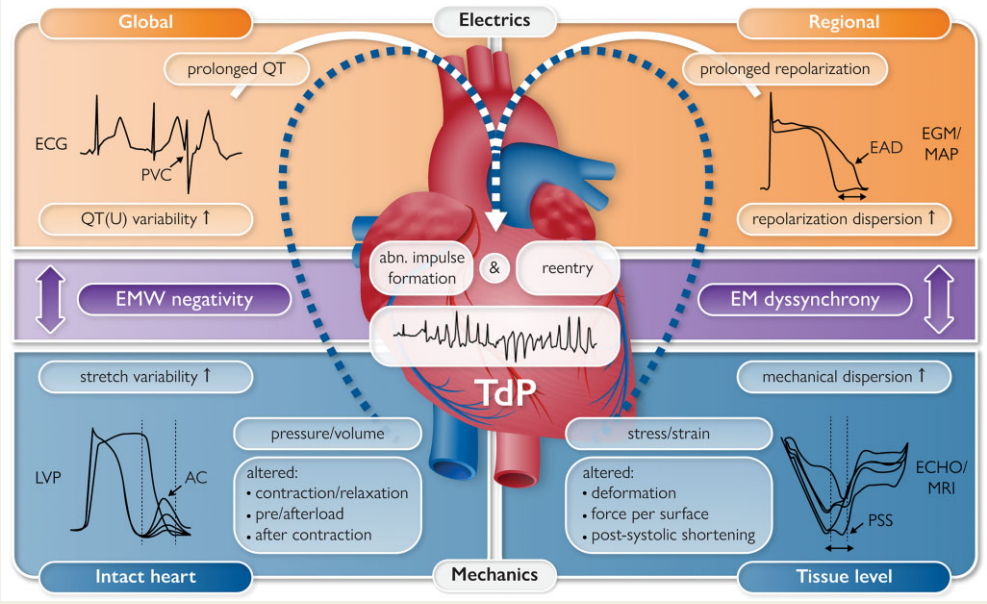

Graphical Abstract Schematic representation of the different global (left) and regional (right) electrical (upper panels) and mechanical (lower panels) components that contribute to electromechanical reciprocity both in the intact heart and at the cardiac tissue level. *Stretch*, passive mechanical stretching of the myocardium caused by changes in volume or pressure load; *stress*, load against which cells actively contract as force per cross-sectional area; *strain*, passive mechanical deformation of tissue/cells normalized to their resting length. ↑, increased; AC, aftercontraction; EAD, early afterdepolarization; EGM, electrogram; EMW, electromechanical window; LVP, left ventricular pressure; MAP, monophasic action potential; PSS, post-systolic shortening; PVC, premature ventricular contraction; TdP, torsades de pointes.

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Abstract

An abundance of literature describes physiological and pathological determinants of cardiac performance, building on the principles of excitation–contraction coupling. However, the mutual influencing of excitation–contraction and mechano-electrical feedback in the beating heart, here designated '*electromechanical reciprocity*', remains poorly recognized clinically, despite the awareness that external and cardiac-internal mechanical stimuli can trigger electrical responses and arrhythmia. This review focuses on electromechanical reciprocity in the long-QT syndrome (LQTS), historically considered a purely electrical disease, but now appreciated as paradigmatic for the understanding of mechano-electrical contributions to arrhythmogenesis in this and other cardiac conditions. Electromechanical dispersion in LQTS is characterized by heterogeneously prolonged ventricular repolarization, besides altered contraction duration and relaxation. Mechanical alterations may deviate from what would be expected from global and regional repolarization abnormalities. Pathological repolarization prolongation outlasts mechanical systole in patients with LQTS, yielding a negative electromechanical window (EMW), which is most pronounced in symptomatic patients. The electromechanical window is a superior and independent arrhythmia-risk predictor compared with the heart rate-corrected QT. A negative EMW implies that the ventricle is deformed—by volume loading during the rapid filling phase—when repolarization is still ongoing. This creates a 'sensitized' electromechanical substrate, in which inadvertent electrical or mechanical stimuli such as local after-depolarizations, after-contractions, or dyssynchrony can trigger abnormal impulses. Increased sympathetic-nerve activity and pause-dependent potentiation further exaggerate electromechanical heterogeneities, promoting arrhythmogenesis. Unraveling electromechanical reciprocity advances the understanding of arrhythmia formation in various conditions. Real-time image integration of cardiac electrophysiology and mechanics offers new opportunities to address challenges in arrhythmia management.

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Keywords Long-QT syndrome • Mechanical function • Mechanical dispersion • Electromechanical reciprocity • Electromechanical window • Arrhythmogenesis

Introduction

Cardiac homeostasis requires the co-ordinated action of billions of cardiomyocytes while continuously adapting to beat-by-beat fluctuations in haemodynamic demand. To this aim, electrical excitation of the myocardium induces mechanical activation (excitation–contraction coupling) in the feedforward loop and, reversely, changes in the heart's mechanical condition affect cardiac electrical activity (mechano-electrical feedback).[1] This mutual influencing of excitation–contraction coupling and mechano-electrical feedback in the beating heart, here designated '*electromechanical reciprocity*', constitutes a continuous process. First hints towards cardiac mechano-electrical influences date back to 1651 when William Harvey reported that '*The pulse has its origin in the blood…the cardiac auricle from which the pulsation starts, is excited by the blood*' (*De Generatione Animalium*).[2] Later, the relevance of critically timed external mechano-electric stressors was recognized for human mechano-electrical feedback, as exemplified by commotio cordis, e.g. by precordially applied thumps.[1] Cardiac-internal mechano-electrical triggers impact through sudden changes in cardiac pressure and/or volume to alter myocardial strain and stress, which may influence depolarization, repolarization, and abnormal impulse formation.[3–6] Indeed, changes in ventricular action potential duration (APD) and the generation of early after-depolarizations (EADs) were observed in patients after pressure increases upon weaning from cardiopulmonary bypass,[7] during transient aortic occlusion,[8] pulmonary balloon valvuloplasty,[9] and the Valsalva manoeuver.[10] Although clinical arguments for stretch-induced arrhythmias are recognized (commotio cordis, infarct border zones, mitral-valve prolapse, and atrial fibrillation)[1,11–13] and experimental evidence is accumulating,[14,15] the exact mechanisms relevant for mechano-induced arrhythmogenesis remain largely unexplained in the beating human heart.

Proarrhythmic consequences of electromechanical reciprocity have been predominantly recognized in the congenital long-QT syndrome (LQTS) caused by gene mutations encoding for ion-channel subunits and ion-channel associated proteins, and historically deemed purely electrical in nature. Indeed, patients with overt LQTS not only demonstrate abnormally long ventricular repolarization/QT interval and spatiotemporal repolarization variability (*Graphical Abstract, upper quadrants*),[16–20] but also global and regional mechanical alterations such as (dispersion of) contraction duration prolongation, altered relaxation and after-contractions (*Graphical Abstract, lower quadrants*).[21–27] Experimental data confirm and expand these observations. In severe cases of LQTS, the disproportionate prolongation of electrical repolarization outlasts the mechanical contraction, reversing the physiological ventricular repolarization–relaxation relation and causing a negative electromechanical window (EMW) (*Figure 1*). Now the aortic valve closes before the T wave ends,[28,29] resulting in abnormal ventricular deformation, due to ventricular loading, when repolarization is still progressing (*Figure 1A*). Although this reversed electromechanical relation was first reported in acquired QT prolongation[30] and in the seminal paper by Jervell and Lange-Nielsen (*Figure 1B*),[31] its arrhythmogenic potential for patients with congenital LQTS was only recognized decades later.[28,29,32]

This review first recapitulates the classical electrical understanding of LQTS pathophysiology, highlighting the importance of global electrical abnormalities, repolarization dispersion, and resultant arrhythmogenesis. Thereafter, the evidence for global mechanical

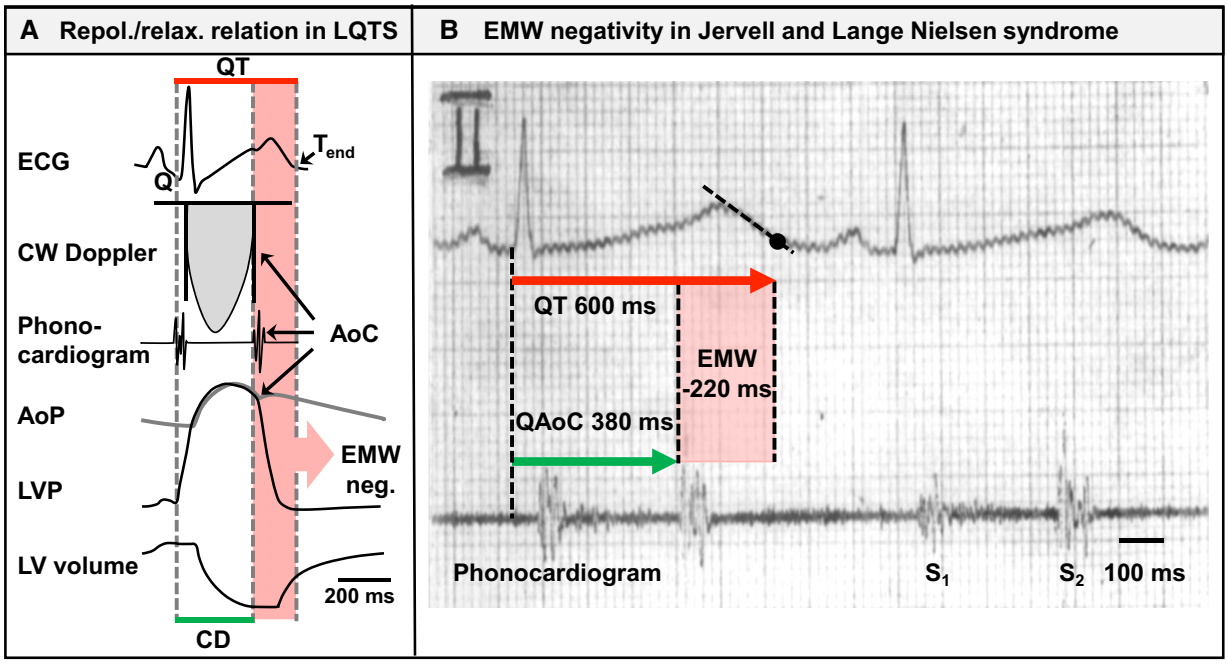

Figure 1 Global electromechanical relations in congenital long-QT syndrome. (*A*) Schematic representation of the temporal relation between whole-heart electrical systole (QT, red line) and derivatives of mechanical systolic duration that underlie global electromechanical window negativity in a hypothetical high-risk long-QT syndrome patient. Various techniques are available to assess contraction duration (CD, green line): continuous-wave Doppler imaging (Q until aortic-valve closure), phonocardiography (S_2), or invasive left ventricular pressure recordings (QAoC or $QLVP_{end}$). Of note, reversed electromechanical relations imply early ventricular filling during the nadir of the T wave. (*B*) Simultaneous electromechanical recording in a 9-year-old boy with Jervell and Lange-Nielsen syndrome and recurrent syncopal events during quinidine treatment from the original publication in 1957.[31] The very negative electromechanical window (−220 ms) heralded the sudden cardiac death that occurred 19 days later. Figure used with permission and modified. AoP, aortic pressure; ECG, electrocardiogram; EMW, electromechanical window; LVP, left ventricular pressure.

alterations and spatiotemporal mechanical dispersion in LQTS is summarized, and clinical arguments for the contribution of electromechanical reciprocity to torsadogenesis are provided. Critical gaps in the clinical insights will be filled with data from intact-animal experiments or *in silico* investigations. Mechanistic insights obtained from the electromechanical interactions in LQTS are paradigmatic for the understanding of arrhythmogenesis in other inherited and acquired conditions such as short-QT syndrome and acquired QT prolongation. A thorough understanding of electromechanical reciprocity will provide novel diagnostic and therapeutic avenues for the management of patients with cardiac arrhythmias, even beyond the LQTS.

Electrical understanding of long-QT syndrome pathophysiology

The congenital LQTS is characterized by prolonged and dispersed cardiac repolarization and is classically deemed a 'purely electrical' disease (*Graphical Abstract, upper quadrants*).[33] Mutations in 17 genes encoding ion-channel subunits or their channel-interacting proteins have been linked to LQTS. Of these, three major and five minor genes have been recently classified as definitely causative,[34] reducing repolarizing outward currents, mostly via loss of function of I_{Ks} (LQT1) or I_{Kr} (LQT2), or augmenting late I_{Na} (LQT3). Distortions of the delicate balance of these ion currents underlie the clinically observed long QT interval. Patients with LQTS are at increased risk of developing life-threatening torsades-de-pointes (TdP) arrhythmias [prolonged repolarization-dependent polymorphic ventricular tachyarrhythmia (VT) with the characteristic, sinusoid-like twisting of the QRS axis around the iso-electric baseline]. Torsades-de-pointes initiation is mostly pause-dependent (±70%, short–long–short, LQT2 and LQT3) or acceleration/non-pause induced (LQT1).[35]

In the classical understanding of torsadogenesis, global and regional electrical perturbations promote abnormal impulse formation and reentrant excitation. Indeed, in the human congenital LQTS, pathological prolongation of repolarization is not uniform, but markedly dispersed in space and time (*Figure 2A*). There is compelling clinical and experimental[36–38] evidence for spatial heterogeneity such as the augmented whole heart (T_{peak}–T_{end}),[39] endocardial inter- and intraventricular,[16,17,19,40] and epicardial gradients of electrical recovery,[20] with differences among the various LQTS genotypes (*Table 1*). Whether *transmural* dispersion of repolarization exists in human LQTS—similarly as observed in experimental *in vivo* models[41,42]—remains to be elucidated. Exaggerated beat-to-beat

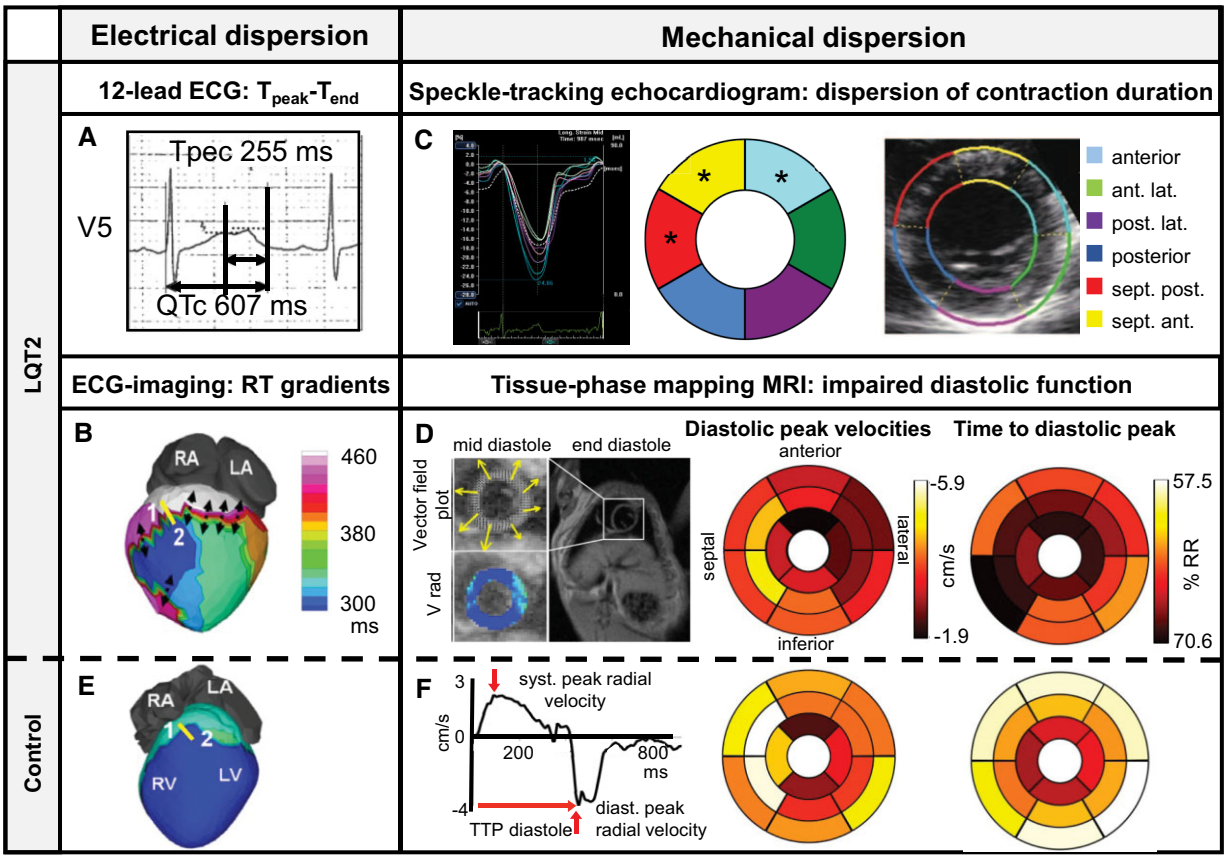

Figure 2 Regional electrical and mechanical dispersion in long-QT syndrome patients with *KCNH2* mutations compared with controls. (*A*) Increased dispersion of repolarization assessed by 12-lead ECG by the T_{peak}–T_{end} interval corrected for heart rate (Tpec). Modified from Takenaka *et al.*[39] (*B*) Steep epicardial recovery-time gradients without genotype-specific patterns by ECG imaging. Modified from Vijayakumar *et al.*[20] (*C*) Increased mechanical dispersion by speckle-tracking echocardiography and (*D*) tissue-phase mapping magnetic resonance imaging techniques: augmented transmural and apicobasal dispersion of left ventricular-contraction duration and an impaired regional diastolic function in LQT2. Modified from Haugaa *et al.*[25] and Brado *et al.*[27] (*E* and *F*) Homogeneous distribution of epicardial relaxation times and uniform left ventricular contraction–relaxation patterns in control subjects. *$P < 0.05$.

variability of repolarization, e.g. short-term QT variability,[18] sudden T(U)-wave alterations,[43] and T-wave alternans[16,44] underscores the importance of temporal repolarization lability. Early afterdepolarizations or delayed afterdepolarizations,[45] occurring spontaneously, after sudden heart-rate changes, or upon swift catecholaminergic surges,[17,40,46] will augment local dispersion of ventricular repolarization (from experimental data[47–52] and computational studies[52,53]) and potentially fuel re-entry. Critically timed premature impulses may arise from steep repolarization gradients ('R-from-T')[53] or from remote regions, 'R-on-T', both propagating unidirectionally away from the repolarization gradient, around a refractory core, and towards the region(s) with late repolarization.[37,51,52,54] Perpetuation of TdP is mostly reentry-based and depends on these gradients.[52,54]

Clinical arrhythmia-risk assessment, of key importance for individualized patient management, currently relies on electrical indices like the QTc, besides clinical (age, gender, prior syncope), genotype- and mutation-specific determinants.[55–59] Symptomatic LQTS patients have, however, also (i) a longer T_{peak}–T_{end} interval, proposed as a surrogate body-surface electrocardiogram (ECG) marker of global spatial dispersion of repolarization,[60,61] (ii) steeper repolarization gradients (using non-invasive electrical mapping techniques),[20] and (iii) increased temporal variability of QT.[18] Despite these clinical observations, these markers of spatial repolarization dispersion are not (yet) routinely used for risk stratification as data are mainly based on relatively small patient cohorts.

Mechanical pertubations in the congenital long-QT syndrome

Evidence of LQTS-associated global and regional (subclinical) ventricular mechanical abnormalities is mounting, bearing mechanistic, and prognostic importance (*Graphical Abstract, lower quadrants*). Since the landmark paper by Jervell and Lange-Nielsen in 1957, various techniques have been employed to investigate the mechanical alterations in the congenital LQTS, such as phonocardiography,[28,31] echocardiography,[21–24,26,29] cardiac magnetic resonance imaging (MRI),[27] and invasive pressure recordings (Figure 1).[62]

Table 1 Electrical, mechanical, and electromechanical parameters important for diagnostic and risk stratification in long-QT syndrome

	Control subjects	LQTS patients	Asympt. LQTS	Sympt. LQTS	Refs
ELECTRICS					
QTc (ms)	391–428 (±22–27)	Diagnostic if QTc > 99th percentile: 470 (m); 480 (f); suspected if QTc > 460	450–462 (±38–44)	488–490 (±43–50)	29,32
Short-term QT variability (ms)	4.1 ± 1.6	6.4 ± 3.2 (in LQT1 + LQT2)	5.4 ± 2.2	9.2 ± 3.9	18
Tpe (ms)	86 ± 20	132 ± 52 (LQT1) 191 ± 67 (LQT2)	Not specified		39
Repolarization (ARI) gradient (ms/cm)	2 ± 2	119 ± 19 92 ± 18 (LQT1) 117 ± 29 (LQT2) 129 ± 14 (LQT3) 137 ± 17 (LQT5)	98 ± 19	130 ± 27	20
MECHANICS					
By echocardiography					
QAoC (ms)		In LQT1 + LQT2 + LQT3 + LQT5 + LQT6 + JLNS			29
	379 ± 31	408 ± 37	405 ± 33	412 ± 42	
CD (ms)		In LQT1 + LQT2 + JLN			25,26
	391 ± 36	426 ± 41 425 ± 37 (LQT1) 418 ± 41 (LQT2)	414 ± 37	442 ± 40	
Dispersion of CD (ms) (~mechanical dispersion)		Whole heart			25,26
	21 ± 7	33 ± 14 31 ± 13 (LQT1) 32 ± 14 (LQT2)	28 ± 12	40 ± 15	
		Longitudinal			
	20 ± 7	36 ± 15	27 ± 12	45 ± 13	
		Circumferential			
	14 ± 11	36 ± 23	26 ± 21	46 ± 22	
GLS (%)	−23 ± 2	−22.1 ± 2.1 −22.4 ± 2.3 (LQT1) −21.4 ± 1.7 (LQT2)	Not specified		26
VRT (ms)	72 ± 11	83 ± 14	84 ± 12	82 ± 16	24,26
E′ (cm/s)	9.8 ± 2.3–12.5 ± 2.0	10.7 ± 2.7	8.8 ± 2	7.9 ± 2	24,26
After-contractions (also by invasive measurements)	—		−/+	++	36,66,70
By TPM-MRI					
TTP_{dia} velocity (ms)		In LQT1 + LQT2 + LQT5			27
		Longitudinal			
	Base: 377 ± 21 Mid: 390 ± 25 Apex: 387 ± 21	Base: 424 ± 41 Mid: 424 ± 41 Apex: 410 ± 45		Not specified	
		Radial			
	Base: 362 ± 23 Mid: 385 ± 27 Apex: 395 ± 21	Base: 424 ± 41 Mid: 424 ± 41 Apex: 424 ± 41		Not specified	

Continued

Table 1 *Continued*

	Control subjects	LQTS patients	Asympt. LQTS	Sympt. LQTS	Refs
Apical peak diastolic velocity (cm/s)		Longitudinal			27
	−5.4 ± 1.7	−3.7 ± 1.1	Not specified		
		Radial			
	−5.9 ± 1.1	−4.8 ± 0.9	Not specified		
Base-apex dispersion of longitudinal TTP_{dia} velocity (ms)	−10 ± 13	+14 ± 15	Not specified		27
ELECTROMECHANICS					
EMW (ms)		In LQT1 + LQT2 + LQT3 + LQT5 + LQT6 + JLNS			
	15–22 (±19–20)	−43 to −25 (±34–46) −43 ± 47 (LQT1) −47 ± 44 (LQT2) −37 ± 47 (LQT3)	−27 to −18 (±29–41)	−67 to −52 (±38–42)	29,32

Specific values for controls and patients with long-QT syndrome, subdivided per affected status are provided. ARI denotes activation–recovery interval. CD, contraction duration; EMW, electromechanical window; GLS, global longitudinal strain; IVRT, isovolumic ventricular relaxation time; JLNS, Jervell and Lange-Nielsen syndrome; LQTS, long-QT syndrome; Tpe, $T_{peak\text{-}end}$; TPM-MRI, tissue-phase mapping-magnetic resonance imaging; TTP_{dia}, time to diastolic peak velocity; QAoC, interval from Q-onset to aortic-valve closure.

Global mechanical alterations

In 1991, using M-mode echocardiography, Nador *et al.*[21] demonstrated that LQTS patients harbour global cardiac mechanical abnormalities, characterized by 'a more rapid early contraction' and 'a slower late wall thickening'. As a result, left ventricular (LV) systolic ejection times prolonged substantially.[21] Such prolonged LV contraction duration, later also shown with tissue-Doppler imaging (TDI),[24] speckle-tracking echocardiography,[25] and MRI[27] was associated with a higher arrhythmic risk in various LQTS cohorts (*Table 1*). Furthermore, mean isovolumic relaxation time was prolonged.[26] Interesting to note, in the setting of a particularly long-QT interval (QTc 800 ms), the onset of polymorphic VTs was preceded by globally impaired systolic and diastolic function.[63] Differences in the extent of mechanical alterations have been observed between patients (and transgenic rabbit models) with LQT1 and LQT2,[64] with less pronounced alterations in LQT1.[26] LQT3 patients had a shorter contraction duration than LQT1 and LQT2 patients despite comparable QTc.[29] Whether these phenomena are mainly due to genotype differences in the *degree* of repolarization prolongation, or whether the underlying ion-channel dysfunction explains the mechanical alterations, remains to be elucidated.

Spatiotemporal mechanical dispersion

In line with the regional heterogeneity of repolarization, the extent to which LV contraction prolongs in patients with LQTS may vary per ventricular-wall segment, i.e. base-to-apex and transmurally (*Figure 2C* and *D*, *Table 1*). This results in an exaggerated LV regional dispersion of contraction duration and of peak strain in LQTS patients compared with healthy controls,[25,26] which appears most pronounced in symptomatic LQT2 subjects.[25] With tissue-phase mapping MRI, the segmental time-to-diastolic peak can be assessed as an indicator of regional contraction–relaxation delays (*Figure 2D*).[27] In nine paediatric LQTS patients, significantly longer longitudinal contraction–relaxation delays were present in the basal, mid, and apicoseptal segments compared with age- and sex-matched healthy subjects.[27] Reduced peak diastolic velocities, hinting to locally dispersed and impaired relaxation, were found in the apex.[27] Furthermore, a reversed sequence of (longitudinal) apex-to-base relaxation became apparent (*Table 1*).[27] Magnetic resonance imaging-based mechanical mapping techniques hold promise especially with regard to assessing the apical mechanical behaviour, a region often difficult to accurately assess by speckle-tracking echocardiography but with a proarrhythmic potential.[65]

Reversed repolarization–relaxation relation

Interestingly, LQTS-associated mechanical aberrancies may deviate from what would be expected from the concomitant global and regional repolarization abnormalities, especially in severe cases of LQTS. As a result of the disproportionate prolongation of electrical repolarization, the aortic-valve closure precedes the T-wave ending by tens of milliseconds (while the opposite is observed in healthy subjects).[28,29] This so-called electromechanical window (EMW) is measured by subtracting the time from the onset of the Q to the closure of the aortic valve recorded with phonocardiography (S2), TDI (closure line in the continuous wave), or the indent of the aortic pressure curve (*Figure 1A*), from the QT interval of the same beat. Although already described in 1957 as the difference in 'electrical and mechanical systole' (*Figure 1B*),[31] the importance of EMW negativity for arrhythmia-risk prediction was only recognized recently (see section 'Electromechanical reciprocity and arrhythmogenesis', *Table 1*).[29,32] The EMW remains relatively constant over time in individuals,[29] but can become exaggerated during instances of electrical instability,[66] sympathetic hyperactivity (as with exercise),[67] or during

isoproterenol infusion,[66] especially in case of an intrinsically weak I_{Ks}. On the contrary, anti-adrenergic measures near-normalize EMW: e.g. left-cardiac sympathetic denervation by shortening the QT[68] and beta-adrenergic receptor blocker treatment by prolonging ventricular contraction duration.[29,69] Experimentally, Ca^{2+}-channel blockade shortened repolarization and prolonged LV-pressure duration, closing the EMW and preventing TdP.[69] Limited clinical data using invasive pressure recordings in a genotype-negative LQTS patient confirm these observations (*Figure 3B*).[62] Further developments of antiarrhythmic properties of electromechanical interventions aiming to restore the abnormal repolarization–relaxation sequence or to normalize regional mechanical perturbations[70] may hold promise for future arrhythmia management.

Electromechanical reciprocity and arrhythmogenesis

Spatiotemporal dispersion of electromechanical interactions renders the heart vulnerable to arrhythmia formation through various mechanisms (*Graphical Abstract*, *Figure 3*).

First, the presence of a negative EMW, as in severe LQTS, implies that the heart is subjected to deformation, by volume loading during the rapid filling phase, when repolarization of the ventricles is still ongoing (*Figure 3C*). This creates a 'sensitized' electromechanical substrate, in which inadvertent electrical or mechanical stimuli such as local afterdepolarizations, aftercontractions, or edging dyssynchrony can trigger abnormal impulses. Indeed, in an experimental setup of isolated blood-perfused canine hearts, the amplitude of stretch-induced monophasic action potential (MAP) afterdepolarizations correlated significantly, within limits, with the rise in LV volume.[14] From that same study,[14] transient clamping of the proximal aorta of *in situ* hearts led to a LV-pressure rise followed by the appearance of MAP afterdepolarizations and premature ventricular complexes (PVCs), the latter often in a pattern of bigeminy. Depending on the timing and magnitude of LV volume or pressure changes, resultant mechano-electric feedback can induce afterdepolarizations, exaggerate repolarization dispersion, and generate ventricular ectopy. Differences in response may depend on variable mechanosensitivity among the myocardial regions. Also, acute changes in preload and mechanical stress by intravenous bolus applications prolonged

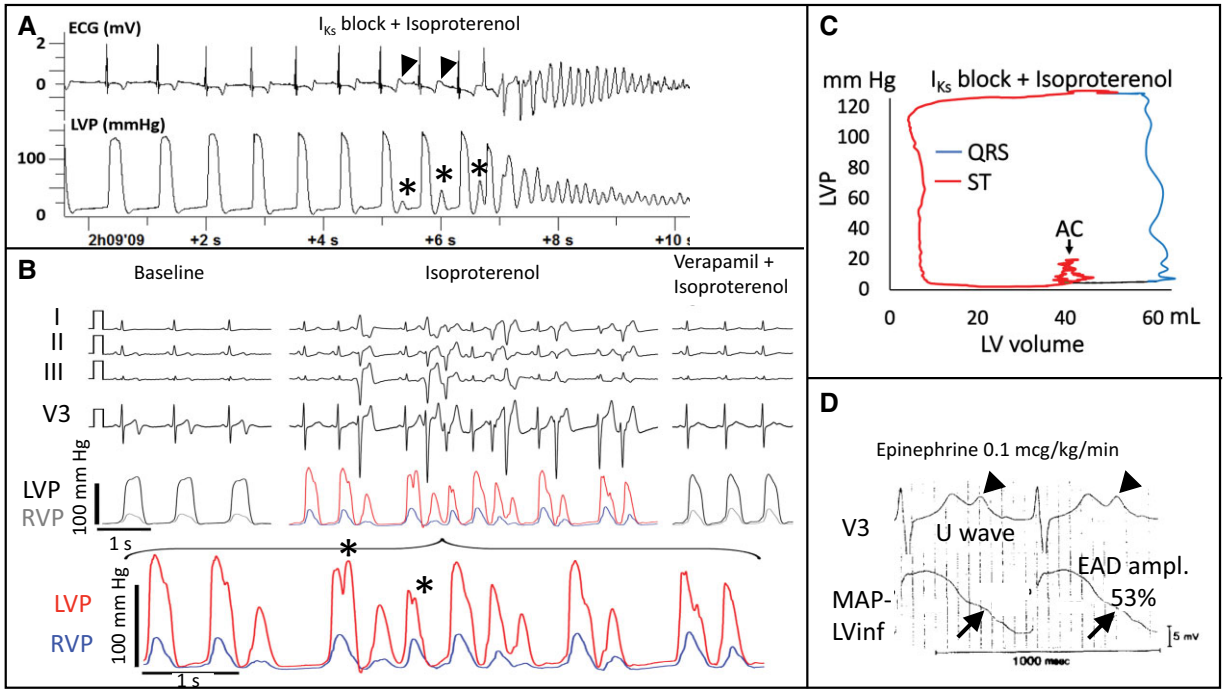

Figure 3 Electromechanical instability during electromechanical window negativity prior to ventricular arrhythmia onset. (*A*) Post-systolic left ventricular aftercontractions (*), mounting in amplitude prior to torsades de pointes onset in an *in vivo* canine drug-induced LQT1 model. The after contractions were paralleled by U-wave formation (triangle) and preceded monophasic action potential-early afterdepolarizations (not shown). Modified from van der Linde.[75] (*B*) Left ventricular arrhythmogenic post-systolic aftercontractions in a genotype-negative long-QT syndrome patient during beta-adrenergic provocation testing with 4 μg/min isoproterenol. Verapamil (10 mg i.v.) completely abolished the electromechanical instabilities. From Moers and Volders.[62] (*C*) Left ventricular pressure–volume loop and simultaneously acquired electrocardiogram and left ventricular pressure recorded in a dog subjected to pharmacologic I_{Ks} blockade + isoproterenol provocation. Note the timing of pressure–volume and left ventricular pressure events compared with the electrocardiogram. AC, aftercontraction. Modified from van der Linde.[75] (*D*) Early after depolarization and U-wave formation in a long-QT syndrome patient during epinephrine provocation testing. No pressure recordings were performed. Modified from Shimizu *et al.*[40]

QTc in both control- and drug-induced LQT2 rabbits, but with larger effects in the latter,[71] implying a higher mechanosensitivity in LQTS. How *global* EMW negativity correlates with *regional* electromechanical reciprocity is currently unknown and requires further in-depth studies. In whole-heart Langendorff experiments, the extent of dispersion of APD correlated with the degree of contraction/relaxation heterogeneities, suggesting an impact of electromechanical reciprocity on the regional level.[64,72] Ultrasound-based electromechanical wave imaging[73] or patient-specific characterization of electromechanical disease substrates through combined clinical and *in silico* modelling[74] may hold promise for the identification of the individual components underlying electromechanical reciprocity. Future developments facilitating non-invasive high-resolution electromechanical mapping may provide novel mechanistic insights and improve patient-specific risk prediction. From experimental studies on drug-induced LQTS, it has become clear that local after contractions and mechanical dyssynchrony are strongly associated with PVCs and TdP initiation (*Figure 3A*).[75] Left ventricular after contractions can occur in the absence of a direct electrical trigger and, in fact, precede concurrent MAP after-depolarizations by tens of milliseconds.[48] Amplitudes with substantial impact, occasionally exceeding 25 mmHg, have been demonstrated, and these mounted in the final beats before TdP onset. Electrocardiogram changes, with T1T2 or TU waves, appeared as electrical footprints of these aftercontractions (*Figure 3A* and *D*).[39] Whether after contractions are also related to arrhythmogenesis in human congenital LQTS is still unclear, but based on case studies with pressure and TDI recordings their presence prior to arrhythmia onset is suspected (*Figure 3B* and *Table 1*).[62,66] Moreover, echocardiographic post-systolic shortenings, which may be related to after contractions, have been observed in symptomatic LQTS patients at rest (*Graphical Abstract, right lower quadrant*).[21,24,25] Whether the site(s) of origin of aftercontractions co-localize with regional mechanical dyssynchrony and/or sites of afterdepolarizations/abnormal impulse formation is currently unknown. Our preliminary results on patients with gene mutations in *KCNJ2*, however, point in that direction.[76] In theory, aftercontractions may impact directly on adjacent myocardium or Purkinje fibres via regional stretching, and remotely through mechanical tethering [77] (*Figure 3C*). Stretch imposed on cardiac Purkinje fibres increases their conduction velocity, without affecting resting membrane potential or APD, [78] and can also induce subthreshold after-depolarizations, PVCs, and ventricular tachycardia.[1]

Secondly, the mechano-electrical substrate and related triggers may be exaggerated by pause-dependent potentiation. Short–long–short cycle-length variations significantly increase the ventricular load and contraction of post-pause beats, besides prolonging repolarization. This is often associated with an increased T_{peak}–T_{end} interval and U-wave amplitude, and even with ventricular ectopy in LQTS patients[79] and experimental models. In one study on LQT2 transgenic rabbits,[80] short–long variation of the rate increased APD dispersion. Importantly, Sauer *et al.* recently demonstrated a link between an increased T_{peak}–T_{end} interval and diastolic dysfunction in unselected (non-LQTS) patients referred for exercise echocardiography.[81] They suggested that abnormal myocardial relaxation is mechanistically associated with increased transmural dispersion of repolarization, indicating that the pause-dependent increase in volume load may potentiate both electrical and mechanical abnormalities in LQTS.

Finally, sudden surges in sympathetic activity, a known arrhythmic trigger in LQTS, cause non-uniform electromechanical responses, such as increased dispersion of repolarization in both human subjects[44,82,83] and experimental models,[38,84,85] also owing to the heterogeneity of cardiac autonomic innervation. While causing positive inotropic and lusitropic effects, adrenergic activation also increases the likelihood of after-depolarizations and aftercontractions (*Figure 3*), and abnormal impulse formation.

On the cellular level, cardiac mechano-electric feedback is primarily carried by cation selective and non-selective stretch-activated channels (SAC_{NS}; reviewed in Refs.[1,86,87]), but also by altered conductivity of voltage-dependent (mechanosensitive) ion channels (for instance I_{CaL}, I_{Ks}, I_{Na}, I_{KATP}), increased myofilament Ca^{2+} sensitivity, and increased sarcoplasmic-reticulum Ca^{2+} release through a higher open probability of ryanodine channels.[1] The electrophysiological impact of mechanical stressors depends on their magnitude and timing (with respect to the phase of the action potential), and on the mechanosensitivity of the myocardium. Given the reversal potential of non-selective stretch-activated channels,[88] early applied systolic stretch (until the beginning of Phase 3 at ~0 to −20 mV) usually accelerates repolarization,[89] whereas later stretch applications elicit repolarization prolongation and potentially mechanically induced 'EADs'.

The QT interval on the surface ECG is a surrogate of *global* ventricular repolarization, but some myocardial regions have shorter APDs and these are already re-excitable during the rapid filling phase, e.g. by stretch due to volume loading. This may elicit mechanically induced 'early afterdepolarizations'. Furthermore, EMW negativity may accentuate regional repolarization dispersion via the aforementioned bimodal (repolarization-shortening vs. -prolonging) stretch effects.

Markers of altered electromechanical reciprocity for risk stratification in long-QT syndrome

Based on the aforementioned, arrhythmia-risk determination in LQTS would benefit from the assessment of alterations in electromechanical heterogeneities and reciprocity, especially in intermediate-risk or genotype-negative LQTS patients, for whom risk assessment is often difficult. Electromechanical window negativity correlates significantly with major arrhythmic events in patients with LQTS and outperforms the QTc as an independent predictor of arrhythmia risk.[29,32] Other parameters indicative of spatiotemporal (electro)mechanical dispersion have also been demonstrated to outperform QTc in small single-center clinical or experimental studies: e.g. prolongation of radial strain in the LV apex was associated with increased arrhythmic risk in a cohort of 47 genotyped LQTS patients.[65] More extensively prolonged time-to-diastolic peak measured by tissue-phase mapping MRI, which indicates contraction–relaxation delays, and a more pronounced mechanical dispersion, was observed in transgenic LQT2 rabbits exhibiting ventricular arrhythmias than in those

without arrhythmia; and proved to be a better risk discriminator than the 'classical' electrical QTc or APD.[90]

From a meta-analysis,[91] the weighted mean difference of various mechanical indices including mechanical dispersion (weighted mean difference 14.9), prolonged contraction duration (weighted mean difference 40.6, ≥430 ms), and EMW negativity (weighted mean difference −26.4, <−59 ms) was put forward. All outperformed QTc (≥460 ms) regarding (intermediate) arrhythmia-risk assessment.[91] This meta-analysis suggested the superiority of LV contraction duration,[91] but no direct head-to-head comparison was made.

Altered electromechanical relations in acquired QT prolongation

Acquired QT prolongation is more prevalent than inherited LQTS. It can be induced by numerous cardiovascular and non-cardiovascular drugs (www.crediblemeds.org) that share the (most-often inadvertent) effect of blocking repolarizing ion currents, such as I_{Kr} or I_{Ks}, or reduce the membrane expression of ion-channel subunits by impairing trafficking from the endoplasmic reticulum to the membrane.[92] Genetic predisposition may favour acquired QT prolongation.[93,94] Alternatively, QT prolongation may occur by electrical remodelling, secondary to pressure or ventricular overload as in structural heart diseases, but also due to endurance sports participation.[95] If mechanical alterations and mechano-electrically induced arrhythmias occur similarly in acquired QT prolongation as in inherited LQTS, these mechanisms may have an even broader impact and relevance for future mechanism-based therapies.

While systematic studies on mechanical perturbations in patients with drug-induced QT prolongation are lacking, a recent case report argues that EMW negativity may be similarly associated with increased risk for TdP as in congenital LQTS.[96] Experimental data on drug-induced QT prolongation in the rabbit (by I_{Kr} blocker E4031; LQT2-like),[72] the dog (I_{Ks} blocker HMR1556 or JNJ-303; LQT1-like),[38,69] and the guinea pig (multiple compounds)[97] indicate that acute (drug-induced) changes in ventricular repolarization cause acute mechanical alterations in contraction duration, diastolic function, and EMW negativity. Mechanical alterations between genetic (chronic) and drug-induced (acute) LQT2 models, however, differ, which suggests that additional remodelling mechanisms (e.g. in Ca^{2+} handling) in chronic LQT states may additionally affect mechanical function.[98] For example, diastolic peak velocities are more affected in longitudinal than in radial direction in drug-induced LQT2 hearts,[64] while in genetic LQTS longitudinal and radial strain are similarly affected.[72] This occurs despite a correlation of (drug-induced or genetic) alterations of electrical function with the extent of reduction of diastolic peak velocities in both.[64,72] Moreover, while systolic function is not changed in transgenic LQT2 rabbits,[72] acute drug-induced QT prolongation increased systolic peak velocities in LQT1 rabbits.[64]

Electrical remodelling in chronic complete atrioventricular conduction block may result in secondary QT prolongation and mechanical alterations such as prolonged isovolumic relaxation times.[99] From experimental chronic atrioventricular block models, temporal differences in electrical and subsequent mechanical remodelling were identified.[100] Serial *in vivo* measurements identified increased end-diastolic myofibre stress and increased ejection strain as primary mechanical alterations, underlying electrical remodelling at least partly.[101] In this experimental model, increased mechanosensitivity was noted upon beat-to-beat preload changes imposed by PR-interval variability.[102] Streptomycin, a non-selective SAC blocker, abolished preload-induced exaggerated temporal dispersion of repolarization. Recent data showed that inherited hypertrophic cardiomyopathy, which is accompanied by acquired QT prolongation, is also paralleled by substantial EMW negativity, which appeared a strong predictor of arrhythmic events.[103]

Moreover, the repolarization abnormalities resulting from strenuous endurance exercise and mechanical stress in some LQTS genotype-negative patients underscore the importance of mechano-electric feedback mechanisms during chronic ventricular load.[95] Detraining, through relieve of chronic mechanical stretch and altered autonomic balance, may normalize QT.[95] Whether detraining also restores electromechanical alterations requires further investigation.

In addition to electrical changes causing mechanical alterations in the context of acquired QT prolongation, mechanical changes may feedback on electrical function, including repolarization. Indeed, several studies that investigated ECG parameters in patients with diseases predisposing to (subclinical) LV-diastolic dysfunction, observed increased T_{peak}–T_{end} intervals[81] and longer QTc in patients presenting with diastolic dysfunction than those without.[104] Likewise, electrical parameters such as (long) QTc and (relative short) T_{end}-P have been proposed as tool for the clinical identification of patients with diastolic dysfunction,[105] hinting towards a similar link between electrical and mechanical alterations as in congenital LQTS. Also, even in healthy individuals, a correlation of longer (but still normal) QTc with increased mechanical dispersion was recently described using strain echocardiography.[106] It remains unclear, however, whether in these diseases electrical alterations precede mechanical alterations or *vice versa*. In preliminary experiments in drug-induced LQT2 rabbit models, acute changes in pre-load that caused changes in mechanical stress prolonged the QTc and increased QT dispersion.[71] Overall, these data indicate that acute changes in myocardial stretch may cause additional alterations of electrical function in acquired LQTS. If these changes exert regionally divergent effects, they may increase proarrhythmic APD heterogeneity and thereby precipitate arrhythmia formation in acquired QT prolongation.

Electromechanical reciprocity in short-QT syndrome

These novel mechanistic and diagnostic insights based on electromechanical profiling in the LQTS are paradigmatic for the understanding of arrhythmogenesis in other conditions. In the context of this review, we will focus on the short-QT syndrome (SQTS) due to its analogy to the LQTS.

The SQTS is an inherited channelopathy, in which gain-of-function mutations in genes encoding for repolarizing K^+ channels or loss-of-function mutations in genes encoding for depolarizing Ca^{2+} channels cause an accelerated cardiac repolarization and hence a shortened QT and APD.[107] Similar to LQTS, SQTS was initially considered a 'purely electrical' disease with normal mechanical function

as exemplified by a normal LV ejection fraction. This concept was challenged, when Frea *et al.*[108] performed tissue-Doppler and speckle-tracking echocardiography in 15 SQTS patients (seven SQT1, three SQT2, and five without known mutation) and identified reduced LV contraction and increased mechanical dispersion compared with healthy controls. Whereas isovolumic contraction and relaxation appeared unaffected (as described previously),[107] systolic ejection time was shortened and global longitudinal strain was reduced (*Figure 4A*). In follow-up analyses,[109] a correlation was found between the short QT interval, mechanical dispersion, and reduced ejection time (*Figure 4B*) and linked to the subclinical systolic dysfunction. A comparable interplay between shortened repolarization and reduced contractile function was found using computational modelling.[110] Reduced intracellular Ca^{2+} transients and reduced active force were observed after incorporation of the SQT1 mutation *KCNH2*-N588K into human ventricular electromechanical computational models. Likewise, shortening of APD reduced ventricular contractile efficiency by more than 60% as compared with normal conditions—due to decreased tension development.[111] Interestingly, when incorporating the *KCNQ1*-S140G mutation to mimic SQT2,[112] pumping efficiency of mutant ventricles was superior to healthy hearts during sinus rhythm despite shortened APD, suggesting potential genotype differences in mechanical function also in SQTS. In transgenic SQT1 rabbit models, we recently identified increased diastolic peak velocities in SQT1 hearts using tissue-phase mapping MRI (*Figure 4A*), indicating facilitated diastolic relaxation in SQT1, while global systolic function, and regional systolic peak velocities were unchanged.[113]

Similar to LQTS, electrical and mechanical changes in SQTS are disproportionate. Contraction duration is not shortened to a similar extent as the shortening of ventricular repolarization, leading to dissociation between the end of ventricular repolarization and the end of mechanical systole. In contrast to LQTS, where the EMW is pathologically negative, in SQTS, it is pathologically positive (in the range of +111 ms[114]—in contrast to +22 ms in healthy subjects) (*Figure 4C*).[29] This holds also for other species, such as kangaroos with a notoriously short QT time,[115] and for drug-induced[116] and transgenic SQTS rabbit models,[113] as well as in *in silico* modelling studies.[110]

Schimpf *et al.*[114] even observed that whereas the end of mechanical systole occurred after the end of the T wave—and hence after the end of ventricular repolarization—it often coincided with a U wave in SQTS patients, suggesting that the U wave is caused by mechano-electric interactions (*Figure 4D*).

The clinical (and experimental) evidence for electromechanical reciprocity as the driving mechanism for arrhythmia formation in SQTS is not (yet) as strong as in LQTS. Several observations, however, suggest such mechanistic role. Two publications on SQTS

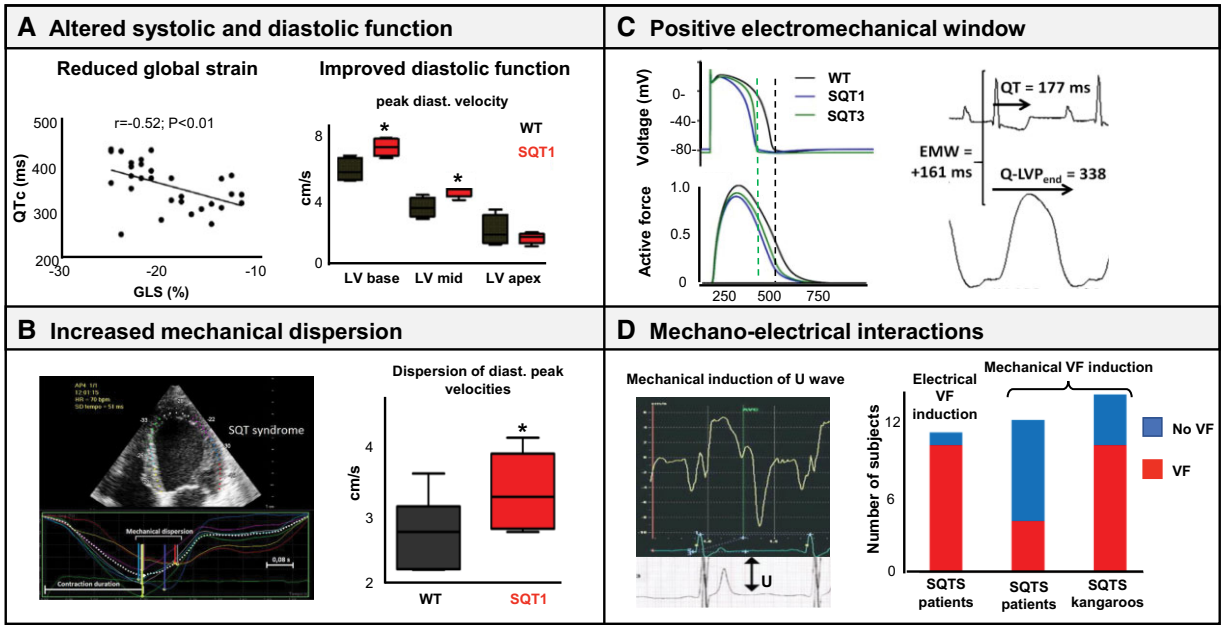

Figure 4 Electromechanical reciprocity in short-QT syndrome. (*A*) Alterations in systolic and diastolic mechanical function assessed by strain echocardiography and tissue-phase mapping magnetic resonance imaging: reduced global systolic strain and improved diastolic function (increased diastolic velocities) in short-QT syndrome patients and SQT1 rabbits. Modified from Frea *et al.*[108] and Odening *et al.*[113] (*B*) Increased mechanical dispersion with regional differences in contraction duration (left) and diastolic peak velocities (right) in short-QT syndrome patients and SQT1 rabbits. Modified from Frea *et al.*[108] and Odening *et al.*[113] (*C*) Shortened action potential duration (left) and shortened QT (right) are accompanied by a near-normal contraction duration (active force, left; Q-LVP$_{end}$, right) resulting in an increased (positive) electromechanical window based on computational modelling and experimental–animal data with drug-induced levcromakalim (0.16 mg/kg i.v.). Modified from Adeniran *et al.*[110] and van der Linde.[75] (*D*) Strain echocardiography indicating a potential mechanical origin of the electrical U wave. Modified from Schimpf *et al.*[114] (left panel). Rate of electrical- and mechanical-induced induction of ventricular fibrillation (right panel). Data from Schimpf *et al.*[107] and O'Rourke *et al.*[115]

describe that the placement of electrophysiological catheters into the right ventricle (RV) or in the epicardial space during invasive studies lead to mechanically evoked PVCs and ventricular fibrillation (VF) induction (which could in the latter case be prevented by local administration of the I_{Na} blocker lidocaine). While, of course, this is no 'physiological' situation, it does indicate that arrhythmia can be easily induced by endocardial and epicardial external mechanical stimuli/alterations. In line with these case reports, Schimpf *et al.*[107] had already described in 2005 that in 3 out of 11 SQTS patients who underwent invasive electrophysiological studies, catheter placement in the RV or LV easily caused mechanically induced VF (*Figure 4D*). While this is in general a very rare event during an electrophysiological study, the fact that 30% of SQTS patients showed this phenomenon may point to an increased electrical vulnerability to mechanical stimuli or alterations in patients with SQTS. Interestingly, this phenomenon has also been reported in the kangaroo, a species with short QT intervals, which has QTc intervals in the range of 260 ms and features of hypertrophic cardiomyopathy. O'Rourke *et al.*[115] described the development of VF in 10/14 anaesthetized kangaroos during catheter placement into the LV (*Figure 4D*).

In addition to this evidence of mechanically induced arrhythmia formation, the above-discussed hypothesis for the mechano-electric origin of the U wave (coinciding with the end of mechanical systole) may also suggest a potential role of intrinsic mechanical alterations/stretch for arrhythmia initiation.[114] If the end of the mechanical systole causes the electrical phenomenon of a U wave, then it can be reasoned that in certain conditions, when mechanically induced electrical changes reach a certain threshold, these may also cause abnormal impulse formation and even VT. Is there any clinical evidence that abnormal impulse formation with a similar (late) timing after the T wave may initiate VT/VF in SQTS? In a comprehensive analysis of VT/VF initiation in 73 SQTS patients,[117] two different types of coupling intervals that initiated the arrhythmia were identified: very short coupling intervals of around 230 ms with PVCs falling into the T wave, and longer coupling intervals of around 350 ms with PVCs that appeared after the end of the T wave—around the time when a U wave could be appreciated on the surface ECG of SQTS patients - suggesting mechanically induced ectopy. Interestingly, in transgenic SQTS rabbits, spontaneous couplets and triplets selectively emerged with a longer coupling interval well after the end of the T wave.[113] Thus far, no mechanical assessments were made at the time of PVC occurrence. These would be important to elucidate a potential temporal relation between mechanical alterations and PVCs.

Concluding remarks

- Cardiac electromechanical reciprocity denotes the mutual influencing of excitation–contraction and mechano-electric coupling in the beating heart.
- External and cardiac-internal mechanical stimuli can trigger electrical responses and arrhythmia depending on the stimulus timing and magnitude, and on the mechano-sensitivity of the myocardium.
- The LQTS, historically considered a purely electrical disease, is characterized by globally and regionally prolonged contraction duration and altered relaxation.
- Reversely, mechanical stress (such as during competitive sports) can cause an acquired mechano-induced QT prolongation in susceptible patients, which is amendable by detraining.
- Changes in mechanical function in LQTS may deviate from what would be expected from global and regional repolarization abnormalities.
- Disproportionately long repolarization can outlast mechanical systole, thus creating a negative EMW.
- Electromechanical window negativity correlates significantly with major arrhythmic events in patients with LQTS and performs better as an independent predictor of arrhythmia risk than QTc alone.
- Pause-dependent increases in ventricular load, besides repolarization prolongation, can evoke regionally different electromechanical responses.
- Likewise, changes in sympathetic activity cause regionally different electromechanical responses, also owing to the heterogeneity of autonomic innervation.
- Exaggerated spatiotemporal electromechanical dispersion, the generation of afterdepolarizations and aftercontractions can contribute to abnormal impulse formation and reentrant excitation.
- Experimental studies indicate that local aftercontractions and local mechanical dyssynchrony are mechano-electric stressors that promote arrhythmogenesis.
- Global and regional mechanics characterized by strain echocardiography or MRI, with the potential of being combined with high-resolution electrical mapping, can improve risk management in patients with LQTS.
- These novel mechanistic and diagnostic insights based on electromechanical profiling in the LQTS are paradigmatic for the understanding of arrhythmogenesis in other inherited and acquired cardiac conditions.
- Multidisciplinary real-time image integration of cardiac electrophysiology and mechanics offers new opportunities to resolve current challenges in arrhythmia management.

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