Cellular and Subcellular Mechanisms of Ventricular Mechano-Arrhythmogenesis

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1 The Cardiac Mechano-Electric Regulatory Loop

The function of the heart is to provide the driving forces needed for the circulation of blood to meet the metabolic demand of the body. This is achieved through an elegant coordination of cardiac electrical excitation and mechanical pumping action. The body's haemodynamic state is continuously adapting, being modulated, for instance, by breathing, postural changes, exercise or circadian oscillations in blood pressure. To facilitate the matching of blood output from the heart to changes in systemic demand, an auto-regulatory system has evolved that intrinsically tethers electrical and mechanical function of the heart through feed-forward ('excitation-contraction coupling', ECC) [1] and feed-back ('mechano-electric coupling', MEC) pathways [2–7]. Together, ECC and MEC form the cardiac mechano-electric regulatory loop, which allows the heart to acutely sense and respond to physiological changes in its intrinsic and external environment and to maintain adequate pump function [1, 5]. In

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M. Hecker, D. J. Duncker (eds.), *Cardiac Mechanobiology in Physiology and Disease*, Cardiac and Vascular Biology 9,
https://doi.org/10.1007/978-3-031-23965-6_11

physiological settings, MEC can have anti-arrhythmic properties, for instance, by reducing dispersion of repolarisation across the ventricles [8, 9]. However, MEC-mediated response to pathophysiological mechanical perturbations, disease-related alterations in the active or passive mechanical state of the heart or changes in factors driving MEC can destabilise cardiac rhythm and contribute to arrhythmogenesis [7, 10–17].

This chapter considers how pathophysiologically altered MEC, combined with changes in the cardiac mechanical environment, contributes to mechanically induced alterations in ventricular electrophysiology that can lead to arrhythmias (hereafter referred to as 'mechano-arrhythmogenesis'). It then discusses cellular and subcellular components of MEC in ventricular cardiomyocytes (CM) that may contribute to ventricular arrhythmogenesis, including mechano-sensitive ion channels (MSC), biophysical signal transmitters (i.e. microtubules, MT) and mechano-sensitive biochemical signalling pathways (i.e. changes in cytosolic free calcium concentration, $[Ca^{2+}]_i$, or reactive oxygen species, ROS). Finally, it describes clinical manifestations of these cellular and subcellular MEC mechanisms in a local (acute regional myocardial ischaemia) and a global (hypertension) pathophysiological setting. Of note, this chapter will not address mechanical modulation of contractility (mechano-mechanical coupling) [18] or stretch effects on sinus rhythm [19, 20], atrial arrhythmias [21] or tissue conduction [22], as the focus is on MEC in ventricular CM.

2 Clinical Evidence and Experimental Studies of Ventricular Mechano-Arrhythmogenesis

Ventricular mechano-arrhythmogenesis requires a sufficiently large and critically timed mechanical stimulus that directly or indirectly activates MSC, and that may be modulated by mechano-sensitive biophysical transmission or biochemical signals. This can be influenced by pathological changes in ventricular MEC, which alter the likelihood that a given stimulus will overcome the threshold for AP induction in CM [5]. While this chapter is focused on CM, it warrants noting that mechano-arrhythmogenesis also involves hetero-cellular interactions with electrotonically coupled cardiac non-myocytes [23] that also express MSC [24]. The contribution of hetero-cellular coupling will be enhanced upon disease-related changes in non-myocyte levels and phenotypes (e.g. myofibroblast conversion), which increase hetero-cellular interactions (for instance, through enhanced intercellular connectivity by increased fibroblast connexin expression) [25] or affect their MSC expression or function [26, 27].

2.1 Clinical Evidence

One of the most dramatic clinical examples of ventricular mechano-arrhythmogenesis is *Commotio cordis*, during which a non-contusional external impact, usually to the precordium, results in rhythm disturbances of variable nature, including ventricular fibrillation [28]. In fact, mechanically induced ventricular fibrillation is one of the leading causes of sudden cardiac death among young athletes and has been one of the primary reasons for which, in many countries, automated external defibrillators are now increasingly located at sporting facilities where potentially deadly impacts to the chest are most likely to occur [29, 30]. Ventricular mechano-arrhythmogenesis is also common during clinical procedures in which contact of medical instruments (e.g. cardiac catheters) with the myocardium causes local tissue deformations that may lead to ectopic excitation and arrhythmogenesis [31–42]. As with precordial mechanical stimulation [43, 44], such device-tissue contact can also revert pre-existing arrhythmias to normal sinus rhythm [5]. Arrhythmogenic changes in ventricular electrophysiology are additionally seen during acute increases in ventricular mechanical load, such as that occurring with balloon valvuloplasty [45] or during surgical manipulations [46–49].

The risk of an abnormal mechanical stimulus triggering an arrhythmia can be enhanced by cardiovascular disease. In patients with established structural heart disease, acute fluctuations in ventricular volume or pressure are more likely to result in premature excitation and sustained tachyarrhythmias [7, 17, 50]. Indeed, arrhythmia incidence in these patients is affected by blood pressure alterations, including those caused by pharmacological interventions [50], circadian oscillations [51] or day-to-day variations [52], such that acute increases in ventricular load (both preload and afterload) are associated with higher rates of arrhythmogenesis. There is also evidence suggesting that local changes in myocardial mechanics play a role in mechano-arrhythmogenesis, as wall motion abnormalities in patients with ischaemic heart disease are associated with an increased prevalence of premature excitation during acute fluctuations in load [16]. Interestingly, this effect also works in reverse: in patients suffering from chronic ventricular volume overload and tachyarrhythmias, acute ventricular unloading can result in termination of ventricular tachyarrhythmias, but alas, often only for as long as the reduction in load can be maintained [53–57].

2.2 Experimental Studies

Existing clinical evidence of ventricular mechano-arrhythmogenesis has been corroborated in experimental studies that have helped to elucidate potential mechanisms. For instance, in the case of *Commotio cordis*, a pig model of baseball impacts to the chest has confirmed historic observations [58, 59] on critical factors for the induction of ventricular fibrillation (such as pre-cordial location and impact with

small and hard projectiles) while adding new information on the link between impact timing and electrophysiological outcomes: while single extra beats can be triggered in diastole, ventricular fibrillation is seen only for impacts in a narrow time-window, ~15–30 ms before the peak T wave of the ECG [60–62]. Isolated heart experiments [63] and computational modelling [64, 65] have further shown that ventricular excitation, induced by a focal mechanical stimulus [66], depends on the degree of myocardial tissue deformation and that it is a local phenomenon (i.e. triggered at the contact site, rather than resulting from the impact-induced intraventricular pressure surge). If a mechanically induced focal excitation overlaps with the trailing wave of the previous regular excitation, it may initiate ventricular fibrillation, highlighting the critical spatio-temporally defined nature of the vulnerable window for mechano-arrhythmogenesis [63].

In addition to elucidating mechanisms of *Commotio cordis*, experimental studies have demonstrated the possibility for acute changes in ventricular load to lead to premature excitation and tachyarrhythmias. Transient increases in intraventricular volume during diastole cause cellular depolarisation, which triggers excitation if supra-threshold [67–84]. Ectopic excitation has also been observed in experiments involving rapid increases in ventricular pressure (due to an acute increase in afterload) [85–87], which has been suggested to be a consequence of enhanced late-systolic myocardial deformation [88]. When an acute ventricular load is applied during systole, it tends to heterogeneously alter repolarisation and refractoriness, furnishing an arrhythmogenic substrate [68–70, 89–111]. In fact, in the isolated heart, an acute increase in intraventricular pressure has been shown to be as arrhythmogenic as the substrate created by the catecholamine-rich milieu and electrical remodeling associated with heart failure [112]. It is important to note that, while changes in intraventricular volume or pressure affect the entire ventricle (whether applied in diastole or systole), the response is generally spatially heterogeneous [113]. This is presumed to be related to variations in myocardial stiffness across the ventricle, such that stretch and the resulting electrophysiological changes are non-uniform [83, 90], with excitation originating from areas of the largest stretch (for instance, in the right ventricular outflow tract) [67, 83, 90].

3 Cellular and Subcellular Mechanisms of Ventricular Mechano-Arrhythmogenesis

Ventricular mechano-arrhythmogenesis in the whole heart arises out of a complex interplay of intra- and intercellular MEC-mediated effects. This next section is focused on the intracellular effects—the cellular and subcellular mechanisms of MEC in ventricular CM, including MSC [24], biophysical signal transmitters [114–116] and biochemical signals [117–121]—and how they shape the effects of MEC at the tissue and organ level.

In ventricular CM, stretch occurring during the resting phase of the cardiac cycle ('electrical diastole') depolarises the sarcolemma. If depolarisation is supra-threshold, this will result in excitation (i.e. it will trigger an action potential, AP). On the other hand, stretch occurring during the AP ('electrical systole') can alter the plateau or affect repolarisation dynamics. As a result, depending on stretch timing, MEC will hasten early phase 3 repolarisation, delay later repolarisation or cause early or delayed afterdepolarisation-like events [68, 69, 89, 90]. Importantly, pathophysiological changes in CM mechanics, electrical activity or factors contributing to MEC may alter this timing dependence while also enabling smaller mechanical stimuli to initiate electrical disturbances [5].

3.1 Mechano-Sensitive Ion Channels

Most acute effects of stretch on ventricular tissue- and CM-level electrophysiology (e.g. diastolic depolarisation, excitation or altered repolarisation) can be explained by MSC [24, 122]. While stretch activated channels (SAC) have been defined exclusively as channels whose activity is directly activated by a mechanical stimulus, MSC also include ion channels whose current is primarily activated by another mechanism (e.g. ligand- or voltage-activated channels), but whose activity can also be mechanically modulated [24, 122]. In fact, it has been suggested that all channels whose opening and closing mechanisms involve changes in their in-plane dimension within the lipid bilayer are MSC and may therefore contribute to MEC [123]. While the exact molecular identity of many MSC in the heart remains a topic of debate, they are generally divided into two groups based on their principal ion permeability. These groups include cation non-specific MSC (MSC_{NS}, which cause depolarisation or altered repolarisation) and potassium (K^+)-selective MSC (MSC_K, which will promote repolarisation [5, 24] and conceivably cause hyperpolarisation in pathological states that are associated with depolarised resting membrane potential, such as ischaemia). There are additional MSC, conducting chloride (Cl^-) ions, which are activated by changes in cell volume (for instance, with osmotic swelling, MSC_{swell}) rather than stretch. They are not believed to contribute to acute MEC-mediated responses, due to a pronounced lag-time in their activation (~ 1 min) and the presumed conservation of cell volume during externally applied deformations of CM [24]. However, in disease states associated with changes in cell volume, such as during cell swelling (e.g. in ischaemia and reperfusion) [124] or CM hypertrophy (where Cl^- channels have been shown to be constitutively active) [125], the contribution of cell volume-sensitive MSC to mechano-arrhythmogenesis may become relevant, for example, by acting as modifiers of the electrophysiological background upon which MEC operates.

3.1.1 MSC_{NS}

With a reversal potential (E_{REV}) between −20 and 0 mV [24], the timing of stretch stimuli (causing MSC_{NS} activation) relative to the AP [122] determines whether MSC_{NS} pass an 'inward' depolarising current (at membrane potentials $< E_{REV}$ of the MSC) or an 'outward' re-/hyperpolarising current (at membrane potentials $> E_{REV}$) [70, 126, 127]. Accordingly, MSC_{NS} can depolarise resting CM. Even though experimental and computational evidence demonstrates stretch-induced depolarisation and AP-induction [67, 71–74, 122], which can be prevented by pharmacological block of MSC_{NS} [69, 73, 75, 76, 92, 128], no single channel patch clamp recordings of MSC_{NS} have been reported in adult ventricular CM. This is possibly due to localisation of MSC in membrane folds (including caveolae and transverse tubules) or at the Z-disc, locations where their direct measurement by the patch clamp method is difficult [24]. It may also relate to a dependence of MSC activation on cytoskeletal elements, the required deformation of which is not engaged in the available experimental systems (i.e. by negative patch pressure) [129]. While this has hindered identification of MSC_{NS} in adult ventricular CM, two groups of ion channels are thought to make important contributions: Piezo and Transient Receptor Potential (TRP) channels [5, 24].

The discovery of Piezo channels generated a great deal of excitement as a potential key MSC_{NS} in CM [130], because Piezo channel kinetics match macroscopic functional observations [24, 131]. However, while it appears that Piezo channels are expressed in macrophages [132] and cardiac fibroblasts [26, 133], only small amounts of Piezo mRNA have been found in cardiac tissue (from mice) [130], and (at the time of writing) no functional Piezo channels have been shown in ventricular CM from any species. Therefore, there is no direct evidence at present for a role of Piezo in ventricular mechano-arrhythmogenesis.

TRP channels are a ubiquitously expressed group of ion channels comprised of six subfamilies, many of which are found in the heart [27]. These channels have garnered interest regarding their role in the pathological progression of hypertrophy, heart failure and ischaemia, as well as in arrhythmogenesis [134, 135]. As TRP channels can pass inward or outward currents at physiological membrane potentials, and some have been shown to be inherently mechano-sensitive [136] (although this is not uncontested [137]), they may yet be found to play an important role in ventricular mechano-arrhythmogenesis.

3.1.2 MSC_{K}

The identity of several MSC_{K} in the heart is well established. TREK-1 and 2 are outwardly rectifying K^+ channels [24]. Being K^+-selective, they pass repolarising currents at all membrane potentials that are naturally experienced by CM. Accordingly, they do not trigger stretch-induced excitation, and their relative contribution to global cardiac MEC phenomena in physiological conditions is

generally believed to be low compared to MSC_{NS} [5]. However, in some diseases, additional mechano-sensitive K^+ currents become available for mechanical activation, making contributions of MSC_K more relevant as the 'net reversal potential' of mechanically induced whole cell current will depend on the relative contributions of MSC_{NS} and MSC_K. In ischaemia, for example, mechano- and adenosine triphosphate (ATP)-sensitive K^+ channels (K_{ATP}) are pre-activated by the reduction in ATP (and increase in ADP) and thus alter MEC-mediated effects on cardiac electrophysiology (considered further in Sect. 4.1) [5, 138–140].

3.2 Biophysical Signal Transmitters

Biophysical signal transmitters, such as MT, relay mechanical cues across the cell, affecting mechano-sensitive cellular components, including MSC and elements responsible for the release (e.g. Ca^{2+} from the sarcoplasmic reticulum, SR, via ryanodine receptors, RyR [118], and from mitochondria [141–145]) or production (e.g. ROS by NADPH oxidase 2, NOX2 [120, 121]) of biochemical signals, which elicit and/or modulate electrophysiological responses [114, 116]. In ventricular CM, MT are particularly important for mechanical transmission [114–116, 118, 120, 146, 147] (although sarcomeric proteins and other cytoskeletal elements not discussed here, such as titin, focal adhesion proteins or integrins, will also be involved [148, 149]).

MT form physical links at the Z-disc through interactions with membrane-associated and intermediate proteins (e.g. desmin) [114]. These links create a rigid scaffold, conferring structural integrity to ventricular CM and facilitating their re-lengthening after contraction [116], as illustrated by transient buckling of MT during cell shortening [150]. MT mechano-transmission is enabled by their load-bearing ability, which is enhanced by their lateral reinforcement [151]. MT load-bearing involves interactions between the intermediate protein desmin and detyrosinated MT [150, 152]. Detyrosination is a post-translational modification that confers MT stability, simultaneously preventing MT degradation and promoting the formation of tight junctions with desmin, resulting in a shift from low-energy sliding to energy-costly buckling of MT during cell contraction [150]. Other, less explored post-translational modifications, such as acetylation, also increase the load-bearing capabilities of MT [146, 153]. Acetylation confers resistance to MT breakage during repetitive mechanical stimulation, resulting in more long-lasting ('aged') MT, which are then available for further post-translational modification [147, 154]. Thus, a denser, more detyrosinated (physically anchored) and/or acetylated (aged) MT network would be expected to enhance mechano-transmission in CM. Indeed, increased detyrosination and acetylation have been shown to enhance mechano-dependent biochemical signalling, such as an increase in the stretch-induced release of Ca^{2+} from the SR (i.e. Ca^{2+} sparks) and NOX2-dependent ROS production [115, 155]. Thus, MT network properties (including post-translational

modifications) warrant exploration for their role in mechano-arrhythmogenesis (explored in Sect. 4.2).

3.3 *Mechano-Sensitive Biochemical Signals*

Mechano-sensitive biochemical signals are by-products of intracellular mechano-transmission and modulate the electrophysiological response of CM to a mechanical stimulus [117, 119, 121]. Principal mediators known to be important for ventricular MEC include mechano-sensitive changes in $[Ca^{2+}]_i$, which is determined by (1) trans-sarcolemmal Ca^{2+} in-/efflux [156, 157]; (2) Ca^{2+} release from/re-uptake into the SR [118, 158, 159]; (3) cytosolic Ca^{2+} buffering (such as by dissociation from/binding to troponin C, TnC [160, 161], or release from/re-uptake into mitochondria [142–145]); and (4) mechano-sensitive changes in ROS [120, 121] (although other important factors exist [119]).

These biochemical signals modulate the activity of ion channels, including TRP ankyrin-1 channels (TRPA1) [162, 163] and K^+-selective Ca^{2+}-dependent channels of big conductance (BK_{Ca}) [26, 164] or other trans-sarcolemmal ion flux pathways, such as the sodium/calcium (Na^+/Ca^{2+}) exchanger (NCX) [156, 157]. At the same time, biochemical signals also affect post-translational modification of MT (e.g. acetylation) [165], which will then affect mechano-transmission (see above) [155]. In this way, whether through interactions with MSC, other trans-sarcolemmal ion flux pathways or biophysical signal transmitters, biochemical signals can modulate ventricular MEC.

3.3.1 Mechano-Sensitive Ca^{2+} Handling

In ventricular CM, the total amount of intracellular Ca^{2+} is affected directly by mechano-sensitive trans-sarcolemmal Ca^{2+} flux or secondarily by the effects of trans-sarcolemmal Na^+ flux on NCX activity [156, 157]. 'Free' cytosolic $[Ca^{2+}]_i$ is additionally affected by the mechano-sensitivity of intracellular Ca^{2+} handling. For instance, increases in $[Ca^{2+}]_i$ occur with mechanically induced Ca^{2+} release from mitochondrial stores (which is independent of sarcolemmal MSC or NCX-mediated Ca^{2+} influx) [142, 143, 145], through a process that is dependent on MT integrity. As a result, MT disruption leads to mitochondrial disorganisation, irregular Ca^{2+} propagation and arrhythmogenic Ca^{2+} waves (which may also involve Ca^{2+} release from the SR) [144]. During contraction, $[Ca^{2+}]_i$ is affected by the mechanical modulation of the affinity of TnC for Ca^{2+}, which is increased during stretch (such that more Ca^{2+} binds to myofilaments) [160]. Upon release of stretch, the rapid dissociation of Ca^{2+} from TnC can cause an arrhythmogenic surge of $[Ca^{2+}]_i$ [161]. In diastole, stretch causes an acute increase in Ca^{2+} spark rate through a MT-dependent mechanism (reduced by MT disruption [118, 158]), suggesting that RyR themselves are in fact (non-sarcolemmal) MSC. This stretch-induced increase in Ca^{2+} spark rate would

be diminished upon cell shortening during contraction and hence result in a negative-feedback mechanism that aids initiation *and* termination of ECC [166].

In physiological conditions, mechano-sensitive Ca^{2+} handling processes interact, presumably synergistically, and control $[Ca^{2+}]_i$. However, pathological alterations in these processes, such as in RyR open probability (for instance, due to oxidation or nitrosylation) [120, 167–169] or in myofilament Ca^{2+} binding affinity [170], may disturb the control of $[Ca^{2+}]_i$, resulting in Ca^{2+}-mediated arrhythmogenesis. This is particularly relevant for diseases associated with altered mechanics [171] or Ca^{2+} overload, such as acute regional ischaemia [156, 172] and hypertension (considered in Sect. 4) [115, 155].

3.3.2 Mechano-Sensitive ROS Production

The stretch-induced increase in Ca^{2+} spark rate is modulated by another mechano-sensitive biochemical signal: ROS [120]. In the context of ventricular MEC, ROS (and any ROS-mediated Ca^{2+} release) is dependent on MT, as increasing MT stability enhances mechanically induced ROS production [115]. This makes it difficult to distinguish between direct and indirect roles of the MT in mechanical modulation of RyR-mediated Ca^{2+} release [118, 120].

Mechanically induced ROS production is graded by stretch magnitude and is more responsive to cyclic than static stretch, which is in keeping with a role during regular cardiac activity [173]. This contributes to the intracellular tuning of Ca^{2+} signalling in response to stretch [120] and to complex intercellular adjustments of contractility (mechano-mechanical coupling [18]) that has been observed in paired muscle ("duplex") studies [174]. This duplex research showed that stretch effects on cellular Ca^{2+}-balance enable CM to adjust their contractility to changes in external demand. It is conceivable that (at least some of the) MEC-mediated responses are a 'side-effect' of this autoregulation of CM mechanical performance. In any case, physiological (e.g. transmural) or pathophysiologically exacerbated heterogeneity in ventricular electro-mechanics (e.g. during ischaemia) may promote arrhythmogenesis via effects on Ca^{2+}-dynamics [175]. For example, a pathological (including mechanically induced) increase in ROS production could contribute to mechano-arrhythmogenesis by sensitising MSC [162, 163] and promoting RyR Ca^{2+} leak [120] while also stabilising MT (through an increase in acetylation) [165]. The latter may be part of a compensatory response (as stiffer CM will be stretched less), but this would come at a cost (requiring higher forces for contraction).

4 Ventricular Mechano-Arrhythmogenesis in Cardiac Disease

One critical determinant of mechano-arrhythmogenesis, as highlighted in Sect. 2, is the spatial nature of a mechanical disturbance. To illustrate this point, we consider two cardiac disease states with spatially divergent alterations in electro-mechanics and different effects on cellular MEC: (1) acute regional myocardial ischaemia, which is focal in nature and involves acute metabolic, electrophysiological and ionic changes that directly alter MEC, and (2) chronic hypertension, which is global in nature and involves chronic cellular remodelling, with secondary effects on MEC.

4.1 Acute Regional Myocardial Ischaemia

Acute regional myocardial ischaemia is a mismatch between the supply and demand of blood in a localised area of the heart, for example, due to occlusion of a coronary artery. Ischaemia is characterised by three hallmark pathophysiological changes to the cellular milieu that drive pro-arrhythmic electrophysiological changes and MEC-mediated responses: (1) reduced interstitial oxygen content (hypoxia); (2) increased extracellular K^+ concentration (hyperkalemia); and (3) decreased intracellular pH (acidosis). This ischaemic milieu (and reduced or lack of blood flow) causes a cardiometabolic shift, which leads to metabolite accumulation and increased osmotic pressure (Fig. 1) [176]. During progression of acute regional myocardial ischaemia, arrhythmias occur in a bi-modal fashion in periods termed ‘phase 1a’ (up to ~10 min following artery occlusion) and ‘1b’ (~15–60 min after occlusion).

The arrhythmias occurring in phase 1a appear to be re-entrant in nature and relate to cellular hyper-excitability. This hyper-excitability is driven by diastolic membrane depolarisation secondary to hyperkalemia, combined with stretch of ischaemic tissue (clinically evident as paradoxical segment lengthening) [177], which activates MSC_{NS}, driving further depolarisation and contributing to premature excitation [176, 178]. In phase 1b, excitability is reduced below normal levels in the central ischemic zone [176, 178], which at the same time begins to stiffen and, thus, resist stretch [179–183]. The particularly high incidence of arrhythmias in this phase has been suggested to instead involve systolic stretch of myocardium at the border between the stiffened ischaemic core and healthy contractile tissue, causing MSC_{NS} and K_{ATP} channel activation [179–183]. In low-flow ischaemia, activation of volume-sensitive MSC through cell swelling caused by increased osmotic pressure may also contribute to electrophysiological changes that promote arrhythmogenesis in both phases (Fig. 1) [124, 125].

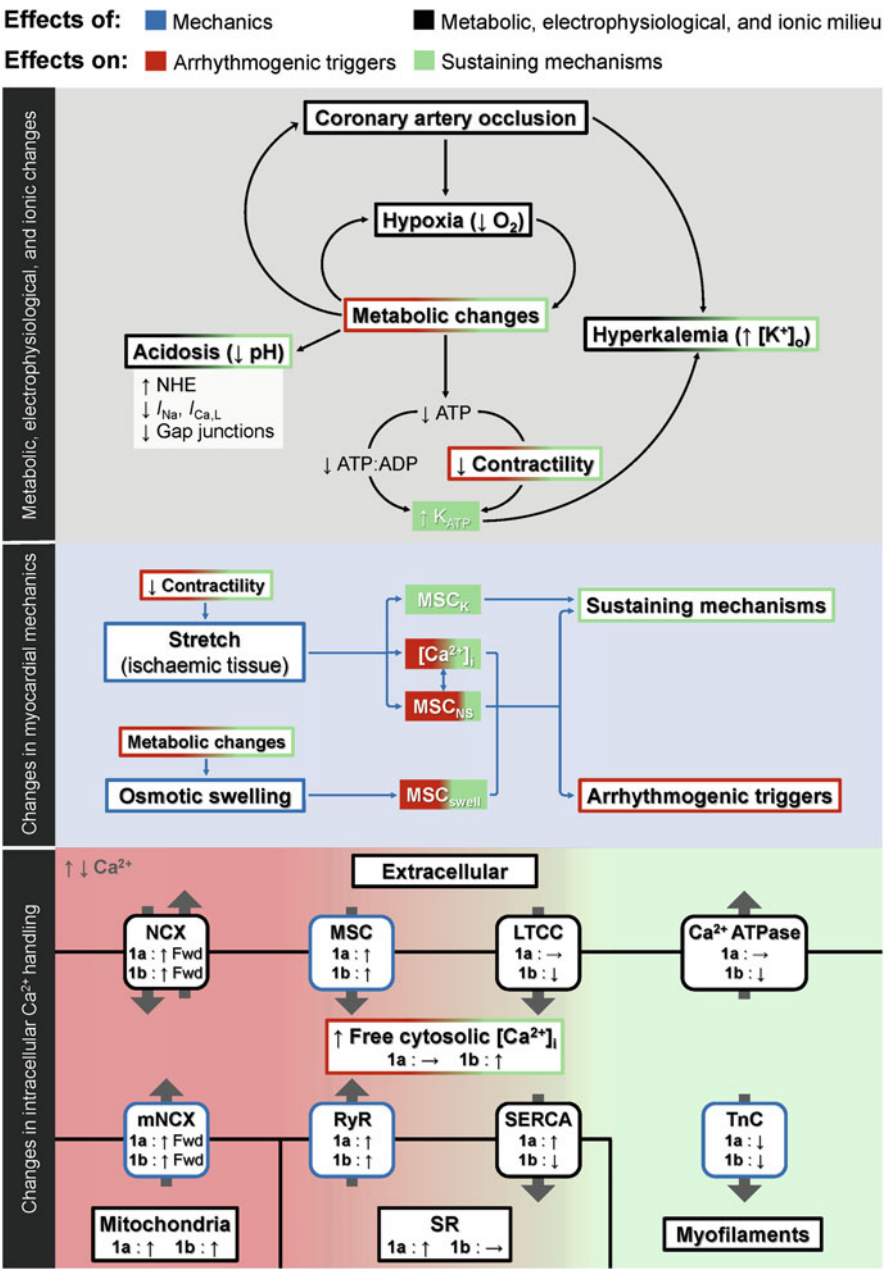

Fig. 1 Cellular and subcellular mechanisms of ventricular mechano-arrhythmogenesis during acute regional myocardial ischaemia. Following coronary artery occlusion, key metabolic, electrophysiological and ionic changes include hypoxia, acidosis and hyperkalemia (black borders, top panel). These changes lead to altered myocardial mechanics through (1) decreased contractility of ischaemic tissue, resulting in stretch of the ischaemic region in phase 1a and of the ischaemic border in phase 1b, and (2) metabolite accumulation, resulting in osmotic swelling (blue borders, middle panel). Stretch activates cation non-specific and potassium (K^+)-selective mechano-sensitive ion

4.1.1 Metabolic, Electrophysiological and Ionic Changes

Hypoxia

Following coronary artery occlusion, reduced blood flow results in tissue hypoxia, causing an increase in anaerobic glycolysis that is concomitant with reduced mitochondrial pyruvate oxidation [26, 184, 185]. This metabolic change leads to an increase in lactate production, metabolite accumulation and a gradual decrease in ATP availability (following exhaustion of cytosolic phosphocreatine reserves that are engaged to initially buffer this change) [186–189] with a simultaneous increase of adenosine diphosphate (ADP). The resulting decrease in the ATP:ADP ratio removes inhibition of mechano-sensitive K_{ATP} channels (Fig. 1) [176]. This has two effects: depolarisation of CM resting membrane potential as a consequence of hyperkalemia and APD shortening due to an increase in outward repolarising K^+ currents. Osmotic swelling, secondary to metabolite accumulation, may also activate volume-sensitive MSC, such as Cl^- channels [124, 125], leading to further resting membrane potential depolarisation and APD shortening. The APD shortening is more pronounced than the reduction in Ca^{2+}-transient duration that also occurs during ischaemia [178], resulting in a period in late repolarisation during which $[Ca^{2+}]_i$ is still high when CM have repolarised. This can facilitate Ca^{2+}-induced re-excitation [13, 190–192]. The degree of APD shortening will be spatially heterogeneous, due to differences in expression [193] and stretch-induced activation of K_{ATP} across the heart [138–140], resulting from regionally differing ventricular mechanics (discussed in more detail below).

Extracellular K^+ Accumulation

The combination of K_{ATP} activation, reduced wash-out of the extracellular space and decreased activity of the Na^+/K^+-ATPase results in hyperkalemia (Fig. 1) [176]. This increase in extracellular K^+ causes a shift in E_{REV} for K^+ toward less negative values,

Fig. 1 (continued) channels (MSC_{NS} and MSC_K, including ATP-sensitive K^+ channels, K_{ATP}) and alters mechano-sensitive calcium (Ca^{2+}) handling processes, leading to an increase in free cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$). At the same time, osmotic swelling activates cell volume-sensitive ion channels (MSC_{swell}). Combined, these mechano-sensitive elements contribute to arrhythmogenic triggering (red borders or shading) and/or sustaining (green borders or shading) effects. Key changes in intracellular Ca^{2+} handling are summarised in the bottom panel. In phase 1a, ATP levels are relatively preserved, so despite increased Ca^{2+} flux into the cytosol, $[Ca^{2+}]_i$ is maintained by normal ATP-dependent extracellular Ca^{2+} extrusion and intra-organelle Ca^{2+} uptake. In phase 1b, ATP levels decrease, so cytosolic Ca^{2+} efflux can no longer balance influx, and there is an increase in $[Ca^{2+}]_i$, which can also trigger and/or sustain arrhythmias. ADP, adenosine diphosphate; $I_{Ca,L}$, L-type Ca^{2+} current; I_{Na}, fast sodium current; $[K^+]_o$, extracellular potassium concentration; LTCC, L-type Ca^{2+} channel; mNCX, mitochondrial NCX; NCX, sodium-Ca^{2+} exchanger; NHE, sodium-hydrogen exchanger; O_2, oxygen; RyR, ryanodine receptors; SERCA, sarcoendoplasmic reticulum ATPase; SR, sarcoplasmic reticulum; TnC, troponin C

resulting in depolarisation of the resting membrane potential of CM. Hyperkalemia also occurs in a bimodal fashion, as in phase 1a, the initial preservation of Na^+/K^+-ATPase activity partially counteracts the K_{ATP}-mediated K^+ efflux. During this period, CM become hyper-excitable, as their slight depolarisation brings the resting membrane potential closer to the threshold for activation of the fast Na^+ channels that underlie AP initiation.

Progressive ATP reduction in phase 1b, however, interferes with Na^+/K^+-ATPase activity, resulting in a greater, secondary rise in extracellular K^+. This leads to further membrane depolarisation, which partially inactivates fast Na^+ channels, thereby reducing cell excitability and prolonging the effective refractory period ('post-repolarisation refractoriness') [178, 194]. In the regionally ischaemic whole heart, the level of extracellular K^+ accumulation differs between the ischaemic core and healthy tissue, due to gradients in extracellular wash-out and in oxygen availability, but in part also due to heterogeneous stretch-induced activation of K_{ATP} in the ischaemic tissue [177]. This gradient results in injury currents that flow from the depolarised ischaemic tissue to the (still electrotonically coupled) healthy tissue, reducing the electrical sink in this region (by shortening the gap between the resting and threshold potential of the electrically coupled healthy myocardium) and contributing to hyper-excitability of tissue at the ischaemic border zone [195, 196].

Intracellular Acidosis

The hypoxia-induced metabolic shift to anaerobic glycolysis, combined with ongoing fatty acid beta-oxidation, enhances proton accumulation and leads to intracellular acidosis. As a result, an initial compensatory efflux of hydrogen through the Na^+/H^+-ATPase (while ATP levels are still sufficient) causes an increase in intracellular Na^+, which reduces Ca^{2+}-extrusion by NCX (or even causes it to operate in reverse mode), leading to intracellular Ca^{2+} accumulation. At the same time, acidosis causes inhibition of fast Na^+ and L-type Ca^{2+} channels [178, 195], along with closure of gap junctions (Fig. 1) [197].

Electrophysiological Changes

At the cellular level, the effects of hypoxia, hyperkalemia and acidosis (as well as osmotic swelling-induced increases in Cl^- currents [124, 125]) manifest as arrhythmogenic changes to the AP: (1) shortened plateau and more rapid repolarisation (resulting in decreased APD and AP triangulation); (2) less negative resting membrane potential; and (3) reduced AP amplitude and upstroke rate [176, 178]. In the regionally ischaemic heart, changes in APD are spatially heterogeneous, with an additional increase in beat-to-beat variability of repolarisation within the peri-infarct region compared to remote, healthy myocardium [198]. This results in dispersion of cell excitability, refractoriness and repolarisation timing, which increases the vulnerability to re-entrant arrhythmias [178, 195, 198].

This arrhythmic risk is further enhanced by increasing the 'excitable gap', i.e. the distance between activation wave-front and wave-end. This occurs though a reduction in APD, and it is enhanced by slowed conduction (due to reduced intercellular coupling and decreased fast Na^+ channel availability). Ventricular conduction may be further slowed by stretch effects, which result in an increase in membrane capacitance [199, 200], caused by the unfolding of membrane invaginations, T-tubule deformation and the incorporation of caveolae into the surface and T-tubule membranes [201, 202].

Alterations in Ca^{2+} Handling

In ischaemia, there is a net increase in cytosolic $[Ca^{2+}]_i$ driven by several mechanisms, including (1) reduced forward-mode NCX activity secondary to the acidosis-induced increase in intracellular Na^+ via the Na^+-H^+ exchanger or stretch-induced (see below) Na^+ entry (and in extreme cases, reverse-mode NCX activity causing Ca^{2+} influx); (2) decreased Ca^{2+} (re-)uptake by the sarco-endoplasmic reticulum ATPase due to reduced ATP levels; (3) an increase in Ca^{2+} leak from the SR, driven by an increase in the open probability of RyR [194]; and (4) stretch effects on Ca^{2+} handling (considered in Sect. 3.3.1). The increase in RyR opening is a result of several effects [176], including Ca^{2+}-induced opening [203], stretch [118, 158] and increased ROS [120]. This overall net gain in intracellular Ca^{2+}leads to an increase in SR Ca^{2+} load. As ischaemia progresses, any compensatory effect of this Ca^{2+} sequestration into the SR is exhausted, further promoting Ca^{2+} leak through RyR and increased $[Ca^{2+}]_i$ (Fig. 1).

4.1.2 Stretch of Ischaemic Myocardium

Altered metabolic, ion channel and Ca^{2+} handling activity in CM during acute regional ischaemia affect myocardial contractility, resulting in regions of diastolic and systolic tissue stretch (Fig. 1).

In phase 1a, there is general stretch of weakened tissue in the central ischaemic region, with additional stretch during mechanical systole. In phase 1b, however, the central ischaemic tissue stiffens, and its stretch is reduced, resulting in stretch of weakened tissue at its border by contraction of adjacent healthy tissue [179–183]. The mechano-arrhythmogenic relevance of ischaemic myocardial stretch is supported by the correlation between wall motion abnormalities and the incidence of ventricular fibrillation seen in patients with coronary artery disease [16]. Experimentally, it has been shown that the onset of tissue stretch and ventricular fibrillation in phase 1a of acute regional ischemia is related [204] and that the degree of tissue stretch is a strong predictor of ventricular fibrillation occurrence [10–12, 177].

In phase 1b, arrhythmia incidence is ventricular load-dependent [13, 14, 80], and aberrant excitation tends to originate at the ischaemic border, where experimental evidence [13, 14] and computational modelling [205] suggest an involvement of

stretch-induced depolarisation mediated by MSC_{NS}. Mechanically induced arrhythmias arising from the ischaemic border will be facilitated by heterogeneous slowing of conduction, due to more pronounced gap junction uncoupling within the ischaemic core than at the ischaemic border [197].

Changes in mechano-sensitive biochemical signalling during ischaemia further facilitate mechano-arrhythmogenesis. For instance, the stretch-induced increase in Ca^{2+} spark rate [118] and ROS production [120] that occurs in healthy tissue is enhanced by ischaemia [172], a response potentially caused by an ischaemia-induced increase in SR Ca^{2+} load [194] or RyR sensitivity [120, 168] or a deficit in the antioxidant capacity of CM [206] (for instance, due to a reduction in the key antioxidant glutathione [207]). In fact, enhancement of mechano-sensitive biochemical signalling in regions of stretched myocardium has been shown to cause focal Ca^{2+} waves [208], which, if occurring at the ischaemic border where the injury current tends to reduce the excitation threshold [195], may contribute an additional trigger or serve as a substrate for sustained mechano-arrhythmogenesis.

4.1.3 Tissue-Level Considerations for Mechano-Arrhythmogenesis in Acute Regional Ischaemia

Mechano-arrhythmogenesis in acute regional ischaemia involves the localised interaction of ischaemia- and stretch-induced electrophysiological effects on CM, generating regionally heterogeneous changes in tissue excitability, refractoriness and electrical conduction. As the acute outcome of myocardial stretch is dependent on its magnitude and timing relative to the background electrical and mechanical activity of CM, ischaemic effects that alter CM electrophysiology—for example, shortening of APD—increase the likelihood that stretch will occur during a period of cellular excitability and, thus, provoke an arrhythmia.

In addition to the MEC effects driven by localised tissue stretch during ischaemia described above, there is also evidence for an increase in MEC itself. This includes an increase in mechano-sensitive biochemical signals (Ca^{2+} sparks, ROS) [172], increased RyR sensitivity (and ensuing Ca^{2+} release) [206] and pre-activation of mechano-sensitive K_{ATP} channels [138–140]. Heterogeneous stretch may therefore lead to regionally differing changes that furnish arrhythmogenic triggers and enhance the substrate for arrhythmia sustenance [162, 163, 209]. The heterogeneous expression of mechano-sensitive [139, 140] K_{ATP} channels [193] (or other MSC_K [210]) across the heart will additionally drive dispersion of repolarisation or cause conduction block [211], favouring re-entrant electrical activity. Finally, mechano-arrhythmogenesis in ischaemia may involve heterogeneous changes in the relative dynamics of membrane voltage and Ca^{2+} transients, which facilitate Ca^{2+}-mediated arrhythmias during late repolarisation [13, 190–192].

4.2 Chronic Hypertension

Chronic hypertension, defined as a sustained increase in systolic (≥130 mmHg) or diastolic (≥80 mmHg) blood pressure [212], results in increased ventricular afterload (i.e. the load against which ventricular CM must contract) [213]. This increase in afterload results in an increase in systolic intraventricular pressure (which maintains ejection), but may also lead to an increase in ventricular preload (i.e. intraventricular volume) if ejection is reduced. The elevated mechanical load experienced by ventricular myocardium in hypertension results in the stimulation of compensatory CM remodelling (although sustained overload ultimately results in decompensated heart failure) [214, 215], which may enhance MEC and contribute to increased mechano-arrhythmogenesis.

Enhanced MEC, secondary to structural and functional remodelling of CM in hypertension, is thought to contribute to the increased incidence of ectopic ventricular excitation in hypertensive patients [17] that occurs during acute fluctuations in ventricular load, including circadian [51] or pharmacologic [50] modulation of blood pressure. This increase in arrhythmogenic triggers may interact with remodelled myocardium, which acts as an arrhythmia-sustaining substrate, contributing to sustained tachyarrhythmias and/or sudden cardiac death [112, 216–221]. Further, mechano-arrhythmogenesis may be enhanced when hypertensive hypertrophic remodelling is complicated by diffusely distributed ischaemic regions (due to wall thickening and microvasculature remodelling [222]) involving mechanisms described in the previous section.

4.2.1 Structural Remodelling

Tissue-level remodelling in hypertension is characterised by concentric thickening of the ventricular wall (hypertrophy), which counteracts the increase in systolic wall stress caused by an increase in systolic intraventricular pressure with elevated afterload. The benefit of this change in chamber geometry is explained by Laplace's law: ($P \sim [T \times m]/R$). An increased intra-ventricular peak pressure (P) can result either from an increase in CM force production (thus raising tissue tension, T)—which, within normal physiological limits, will be afforded by length-dependent activation of force generation (Frank-Starling law of the heart [223])—or from an increase in ventricular wall thickness (m, hopefully in the absence of an increase in chamber radius, R, which would worsen the situation). Increases in sarcomeric force production are limited in scope, so in pathological settings the increase in ventricular wall thickness accounts for the necessary increase in intra-ventricular pressure (P). This is the result of the parallel addition of sarcomeres in CM, thereby increasing cell diameter, as opposed to their addition in series—which would increase cell length and increase chamber radius (although with prolonged hypertension this may also occur)—or the addition of new cells (CM division is exceedingly uncommon in the adult mammalian heart [224]). The degree of

concentric hypertrophy thus scales with the increase in pressure, resulting in a normalisation of wall stress, along with an increase in the ratio of wall thickness to inner chamber diameter [214, 215].

Microtubule Network

In addition to ventricular wall thickening, chronic hypertension is associated with remodelling of the cytoskeleton, characterised by changes in the density (via polymerisation) and stability (via post-translational modifications, altered intermediate protein linkages and changes in expression of MT-associated proteins) of the MT network [225, 226]. These changes to the MT network may work to reduce CM stretch, which would occur if ventricular preload is increased.

While clinical observations [227, 228] and experimental models [229, 230] have demonstrated that an increase in MT density occurs in hypertension, it has remained unclear whether MT proliferation begins during compensatory hypertrophy or is a consequence of the transition to decompensation (discrepancies in published reports may relate to inconsistencies between hypertensive models used, both in terms of species and method to induce hypertension) [231]. Regardless of the moment of onset, the MT network has been consistently shown to become denser and more stable in hypertension [227–230, 232, 233]. MT network remodelling appears to contribute to altered CM shortening and relaxation: hyper-polymerisation of MT in healthy cells decreases contraction and relaxation, while MT de-polymerisation in failing CM results in an improvement [116, 234, 235]. The relative contribution of an increase in the rate of MT polymerisation (which would present as an overall increase in tubulin content) versus an enhanced stability of existing MT (which would manifest as post-translationally modified 'aged' MT) to these effects remains to be clarified [114, 116, 153, 228].

Microtubule Post-Translational Modifications

During contraction, MT buckle at wavelengths corresponding to the distance between adjacent sarcomere units [150]. This process, which also enhances viscoelastic resistance, is dependent on the level of detyrosination, a post-translational modification of α-tubulin that involves the removal of the C-terminal tyrosine, which exposes a glutamate at the newly formed C-terminus [146, 236]. This suggests that the load-bearing (and, by extension, contribution to mechano-transmission) and re-lengthening (which is resisted by viscous forces) [116] of MT are affected by detyrosination, rather than MT density alone. Therefore, pathological increases in the level of MT detyrosination in hypertension may have profound effects on chamber relaxation (which would affect passive ventricular filling during early diastole) [237, 238], ventricular MEC and, as a result, mechano-arrhythmogenesis.

MT detyrosination confers stability to the MT network by preventing the breakdown of existing MT and by facilitating cross-linking with intermediate proteins

[114, 239, 240] (e.g. desmin [150, 152]). This results in a shift from low resistance MT sliding to high-energy buckling during contraction, which modulates the effect of MT on mechano-transmission and segment re-lengthening (by increasing viscoelastic resistance) [116, 150, 228]. In human [228] and murine CM [115], inhibition of detyrosination increases the wavelength and disrupts the organisation of MT buckling (suggesting an attenuation of their resistance to compression and load-bearing capability), which is associated with an increase in the velocity of cellular contraction and relaxation, presumably due to reduced viscoelastic resistance. Conversely, enhancing detyrosination (without a change in MT density) increases both cell stiffness and viscosity, with an associated decrease in contraction and relaxation velocity [115, 150]. This suggests that in ventricular CM subjected to pressure overload, enhanced detyrosination, rather than enhanced MT density, accounts for increased stiffness and impaired contraction and relaxation kinetics. Indeed, in addition to the overall increase in MT detyrosination in failing human CM, there is upregulation of a gene encoding a pre-detyrosinated tubulin [228], as well as of the detyrosination promoting MT-associated protein 4 (MAP4) [241]. As a consequence, suppression of detyrosination in CM from pressure overload patients improves contractile and relaxation function, and the degree of such improvement scales with initial CM stiffness [150, 228].

MT detyrosination is promoted by interactions with MT-associated and intermediate proteins, such as MAP4 [228, 241, 242] and desmin [150, 152]. In pressure overload, there is upregulation of MAP4 (which occurs early in hypertrophy and stabilises MT by preventing their degradation [241]) and desmin, both of which contribute to the pathologic increase in detyrosination levels. Desmin is known to bind specifically to detyrosinated tubulin and facilitate its buckling behaviour [150, 152]. The increase in desmin expression in pressure overload, however, is partially comprised of an isoform prone to misfolding and aggregation [228], which probably explains observations of MT and desmin misalignment [114, 228, 243]. Such MT disorganisation would contribute to decompensated heart failure, including detrimental effects on trafficking of sarcomere precursors, thereby limiting compensatory hypertrophy [114, 244–246].

4.2.2 Proposed Mechanisms of Mechano-Arrhythmogenesis in Hypertension

One function of the MT network is the transmission of mechanical signals across CM [116], which is enhanced by increases in its density or stability (e.g. through detyrosination or acetylation) [114]. Pathophysiological alterations in the MT network may be arrhythmogenic if they modulate MSC activity (which has been demonstrated experimentally by modulation of detyrosination [115] and acetylation [155]), by changing the degree of mechanical stimulation MSC experience (either by reducing the dampening effect of the MT or by enhancing mechano-transmission) [24, 129, 247] or by sensitising MSC [134, 162, 163] (through an increase in MT-dependent biochemical signal production [115, 155]).

In hypertension, remodelling of the CM cytoskeleton results in a laterally reinforced MT network (via interactions between detyrosinated tubulin, desmin and MAP4) [114]. Increased lateral reinforcement facilitates the load-bearing and, thus, biophysical signal transmission capability of the MT network [151]. The remodelled cytoskeleton will thus increase MEC, through an increase in mechano-sensitive biochemical signal production with increased levels of detyrosination [115] and contribute to the constitutive activation of volume-sensitive Cl^- channels following transition to failure [248]. An increase in MEC would be expected to reduce the magnitude of CM stretch needed to cause excitation and trigger an arrhythmia. A role for MT in increased mechano-arrhythmogenesis has been corroborated in several experimental models, including one in which an acute pharmacologically induced rise in MT proliferation and detyrosination in the whole heart (with paclitaxel) was associated with an increased prevalence of acute volume pulse-induced mechano-arrhythmogenesis [81]. However, it should be noted that in this study, potential confounding effects of increased peak intraventricular pressure, associated with volume injections into stiffened ventricles, cannot be excluded (relevant data was not reported).

Enhanced mechanically induced ROS production in hypertension, promoted by elevated levels of detyrosination [115], would be further increased by upregulation of NOX2 [249]. This elevated level of ROS may promote an arrhythmogenic intracellular milieu (i.e. elevated $[Ca^{2+}]_i$ levels) through, for example, increased Ca^{2+} leak from the SR [120, 169]. ROS and Ca^{2+} also modulate the activity of MSC, [162, 163] whose intracellular trafficking and stretch activation may be affected by alterations of the MT network in hypertension [24]. As such, pathological remodelling of biophysical signal transmitters and the resultant effect on ventricular MEC may contribute to formation of arrhythmic triggers and a substrate for mechano-arrhythmogenesis in hypertension.

5 Conclusion

The heart is an electrically controlled mechanical pump with intricate feedback mechanisms that dictate the heart's response to acute changes in its mechanical environment. At the cellular level, these MEC effects involve mechano-sensitive components, including MSC [24], biophysical signal transmitters (e.g. the MT network [114]) and mechano-sensitive biochemical signals [117, 119, 121] (e.g. intracellular ROS and Ca^{2+} [118, 120]). In this chapter, we have discussed how these cellular and subcellular components of MEC in ventricular CM contribute to tissue-level ventricular mechano-arrhythmogenesis.

The potential for a mechanical change to elicit an electrical response depends on the timing of the associated mechanical stimulation relative to the AP and on its magnitude and rate of rise [5]. Therefore, disease states in which regional (e.g. ischaemia [172]) or global (e.g. hypertension [114, 236]) mechanical alterations occur and which are associated with changes in AP dynamics (altering the relative

duration of systolic and diastolic periods [13, 134]) or changes in MEC (altering the threshold for stretch-induced excitation [7, 15, 17, 112]) may make the heart more prone to mechano-arrhythmogenesis. In these cases, mechanically induced excitation constitutes an arrhythmogenic trigger, which interacts with a disease-mediated pro-arrhythmic substrate and converts into sustained arrhythmic activity [17, 134].

The nature of metabolic, electrophysiological and ionic changes, as well as MT network remodelling affecting MEC, will vary across cardiac diseases. When considering the relative contribution of cellular and subcellular mechanisms to ventricular mechano-arrhythmogenesis identified in this chapter, it is essential to assess the precipitating factors of the disease being studied, as well their structural and functional manifestations. Comparison of diseases with differences in mechanical loading (e.g. ventricular volume versus pressure overload) or structure-function remodelling (heart failure with preserved versus reduced ejection fraction) will provide critical insight into how disease-induced alterations in cellular MEC drive ventricular mechano-arrhythmogenesis.

For instance, while pressure overload is characterised by densification and increased detyrosination of the MT network, resulting in an increase in MEC, in volume overload there is a reduction in detyrosination-desmin interactions and a disruption of cytoskeletal integrity [243], such that the influence of the MT network on MSC and biochemical signals may be attenuated. Effects of volume overload on MEC may in fact more closely resemble those seen in acute ischaemia (tissue stretch- [177] and osmotic CM swelling-induced [124, 125] MSC activation), but over the entire ventricle (globally), rather than regionally varying (local). In both cases it would be attractive to determine whether a stretch-induced increase in biochemical signalling (i.e. Ca^{2+} sparks and ROS production) involves alterations in post-translational modifications of MT and whether this increases MSC sensitivity.

In failing human CM, both contraction and relaxation are improved by suppression of MT detyrosination [228]. CM from patients with heart failure with preserved ejection fraction, however, show a greater improvement than those with reduced ejection fraction, suggesting there is a greater contribution of detyrosination to the reduced mechanical function in those cells. Thus, it would be informative to compare MEC and mechano-arrhythmogenesis between those two forms of heart failure.

In summary, this chapter has discussed cellular and subcellular mechanisms contributing to mechano-arrhythmogenesis in ventricular CM, with a focus on two disease states that highlighted local (e.g. acute regional ischaemia) and global (e.g. hypertension) pathological manifestation relevant for MEC. The intricate interaction between the various components of ventricular MEC contribute to formation of both triggers and substrate for arrhythmogenesis. Understanding the precise interactions of these components is necessary to facilitate the development of a mechanistic framework for understanding how therapies targeting MEC may contribute to the prevention of ventricular mechano-arrhythmogenesis.

Compliance with Ethical Standards

Funding This work was supported by the Canadian Institutes of Health Research (MOP 342562 to T.A.Q.), the Natural Sciences and Engineering Research Council of Canada (RGPIN-2016-04879 to T.A.Q.) and the Heart and Stroke Foundation of Canada (National New Investigator Award to T. A.Q.). BAC and PK are members of the German Research Foundation Collaborative Research Centre SFB1425 (422681845).

Conflict of Interest All authors declare they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Bers DM (2002) Cardiac excitation–contraction coupling. Nature 415:198–205. https://doi.org/10.1038/415198a
2. Kohl P, Ravens U (2003) Cardiac mechano-electric feedback: past, present, and prospect. Prog Biophysics Mol Biology 82:3–9. https://doi.org/10.1016/s0079-6107(03)00022-1
3. Kohl P, Sachs F, Franz MR (eds) (2011) Cardiac Mechano-electric coupling and arrhythmias, 2nd edn. Oxford University Press, Oxford
4. Quinn TA, Kohl P, Ravens U (2014) Cardiac mechano-electric coupling research: fifty years of progress and scientific innovation. Prog Biophysics Mol Biology 115:71–75. https://doi.org/10.1016/j.pbiomolbio.2014.06.007
5. Quinn TA, Kohl P (2021) Cardiac mechano-electric coupling: acute effects of mechanical stimulation on heart rate and rhythm. Physiol Rev 101:37–92. https://doi.org/10.1152/physrev.00036.2019
6. Ravens U (2003) Mechano-electric feedback and arrhythmias. Prog Biophysics Mol Biology 82:255–266. https://doi.org/10.1016/s0079-6107(03)00026-9
7. Taggart P, Sutton PMI (1999) Cardiac mechano-electric feedback in man: clinical relevance. Prog Biophysics Mol Biology 71:139–154. https://doi.org/10.1016/s0079-6107(98)00039-x
8. Opthof T, Meijborg VMF, Belterman CNW, Coronel R (2015) Synchronization of repolarization by mechano-electrical coupling in the porcine heart. Cardiovasc Res 108:181–187. https://doi.org/10.1093/cvr/cvv140
9. Quinn TA (2015) Cardiac mechano-electric coupling: a role in regulating normal function of the heart? Cardiovasc Res 108:1–3. https://doi.org/10.1093/cvr/cvv203
10. Barrabés JA, Garcia-Dorado D, González MA et al (1998) Regional expansion during myocardial ischemia predicts ventricular fibrillation and coronary reocclusion. Am J Physiology-Heart Circ Physiol 274:H1767–H1775. https://doi.org/10.1152/ajpheart.1998.274.5.h1767
11. Barrabés JA, Garcia-Dorado D, Padilla F et al (2002) Ventricular fibrillation during acute coronary occlusion is related to the dilation of the ischemic region. Basic Res Cardiol 97:445–451. https://doi.org/10.1007/s003950200051
12. Barrabés JA, Inserte J, Agulló L et al (2015) Effects of the selective stretch-activated channel blocker GsMtx4 on stretch-induced changes in refractoriness in isolated rat hearts and on ventricular premature beats and arrhythmias after coronary occlusion in swine. PLoS One 10: e0125753. https://doi.org/10.1371/journal.pone.0125753
13. Baumeister PA, Lawen T, Rafferty SA et al (2018) Mechanically-induced ventricular arrhythmias during acute regional ischemia. J Mol Cell Cardiol 124:87–88. https://doi.org/10.1016/j.yjmcc.2018.07.021

14. Coronel R, Wilms-Schopman FJG, deGroot JR (2002) Origin of ischemia-induced phase 1b ventricular arrhythmias in pig hearts. J Am Coll Cardiol 39:166–176. https://doi.org/10.1016/s0735-1097(01)01686-2
15. Sideris DA (1993) High blood pressure and ventricular arrhythmias. Eur Heart J 14:1548–1553. https://doi.org/10.1093/eurheartj/14.11.1548
16. Siogas K, Pappas S, Graekas G et al (1998) Segmental wall motion abnormalities alter vulnerability to ventricular ectopic beats associated with acute increases in aortic pressure in patients with underlying coronary artery disease. Heart 79:268. https://doi.org/10.1136/hrt.79.3.268
17. Sutherland GR (2017) Sudden cardiac death: the pro-arrhythmic interaction of an acute loading with an underlying substrate. Eur Heart J 38:2986–2994. https://doi.org/10.1093/eurheartj/ehw449
18. Quinn TA, Kohl P (2016) Rabbit models of cardiac mechano-electric and mechano-mechanical coupling. Prog Biophysics Mol Biology 121:110–122. https://doi.org/10.1016/j.pbiomolbio.2016.05.003
19. Quinn TA, Kohl P (2012) Mechano-sensitivity of cardiac pacemaker function: pathophysiological relevance, experimental implications, and conceptual integration with other mechanisms of rhythmicity. Prog Biophysics Mol Biol 110:257–268. https://doi.org/10.1016/j.pbiomolbio.2012.08.008
20. MacDonald EA, Quinn TA (2021) What keeps us ticking? Sinoatrial node mechano-sensitivity: the grandfather clock of cardiac rhythm. Biophys Rev 13:707–716. https://doi.org/10.1007/s12551-021-00831-8
21. Ravelli F (2003) Mechano-electric feedback and atrial fibrillation. Prog Biophysics Mol Biol 82:137–149. https://doi.org/10.1016/s0079-6107(03)00011-7
22. Pfeiffer ER, Tangney JR, Omens JH, McCulloch AD (2014) Biomechanics of cardiac electromechanical coupling and Mechanoelectric feedback. J Biomech Eng 136:021007. https://doi.org/10.1115/1.4026221
23. Quinn TA, Camelliti P, Rog-Zielinska EA et al (2016) Electrotonic coupling of excitable and nonexcitable cells in the heart revealed by optogenetics. Proc National Acad Sci 113:14852–14857. https://doi.org/10.1073/pnas.1611184114
24. Peyronnet R, Nerbonne JM, Kohl P (2016) Cardiac mechano-gated ion channels and arrhythmias. Circ Res 118:311–329. https://doi.org/10.1161/circresaha.115.305043
25. Baudino TA, Borg TK (2011) The origin of fibroblasts, extracellular matrix, and potential contributions to cardiac mechano-electric coupling. In: Kohl P, Sachs F, Franz MR (eds) Cardiac Mechano-electric coupling and arrhythmias, 2nd edn. Oxford University Press, Oxford, pp 138–142
26. Jakob D, Klesen A, Allegrini B et al (2021) Piezo1 and BKCa channels in human atrial fibroblasts: interplay and remodelling in atrial fibrillation. J Mol Cell Cardiol 158:49–62. https://doi.org/10.1016/j.yjmcc.2021.05.002
27. Hof T, Chaigne S, Récalde A et al (2019) Transient receptor potential channels in cardiac health and disease. Nat Rev Cardiol 16:344–360. https://doi.org/10.1038/s41569-018-0145-2
28. Kohl P, Nesbitt AD, Cooper PJ, Lei M (2001) Sudden cardiac death by commotio cordis: role of mechano—electric feedback. Cardiovasc Res 50:280–289. https://doi.org/10.1016/s0008-6363(01)00194-8
29. Maron BJ, Doerer JJ, Haas TS et al (2009) Sudden deaths in young competitive athletes. Circulation 119:1085–1092. https://doi.org/10.1161/circulationaha.108.804617
30. Maron BJ, Estes NAM (2010) Commotio cordis. New Engl J Medicine 362:917–927. https://doi.org/10.1056/nejmra0910111
31. Bõhm A, Pintér A, Préda I (2017) Ventricular tachycardia induced by a pacemaker lead. Acta Cardiol 57:23–24. https://doi.org/10.2143/ac.57.1.2005375
32. Damen J (1985) Ventricular arrhythmias during insertion and removal of pulmonary artery catheters. Chest 88:190–193. https://doi.org/10.1378/chest.88.2.190

33. Elliott CG, Zimmerman GA, Clemmer TP (1979) Complications of pulmonary artery catheterization in the care of critically iii patients a prospective study. Chest 76:647–652. https://doi.org/10.1378/chest.76.6.647
34. Fiaccadori E, Gonzi G, Zambrelli P et al (1996) Cardiac arrhythmias during central venous catheter procedures in acute renal failure: a prospective study. J Am Soc Nephrol 7:1079–1084. https://doi.org/10.1681/asn.v771079
35. Iberti TJ, Benjamin E, Gruppi L, Raskin JM (1985) Ventricular arrhythmias during pulmonary artery catheterization in the intensive care unit prospective study. Am J Medicine 78:451–454. https://doi.org/10.1016/0002-9343(85)90337-7
36. Kusminsky RE (2007) Complications of central venous catheterization. J Am Coll Surgeons 204:681–696. https://doi.org/10.1016/j.jamcollsurg.2007.01.039
37. Lee JC, Epstein LM, Huffer LL et al (2009) ICD lead proarrhythmia cured by lead extraction. Heart Rhythm 6:613–618. https://doi.org/10.1016/j.hrthm.2009.01.039
38. Lee T-Y, Sung C-S, Chu Y-C et al (1996) Incidence and risk factors of guidewire-induced arrhythmia during internal jugular venous catheterization: comparison of marked and plain J-wires. J Clin Anesth 8:348–351. https://doi.org/10.1016/0952-8180(96)00083-9
39. Lindsay AC, Wong T, Segal O et al (2006) An unusual twist: ventricular tachycardia induced by a loop in a right ventricular pacing wire. Qjm Int J Medicine 99:347–348. https://doi.org/10.1093/qjmed/hcl043
40. Michel J, Johnson AD, Bridges WC et al (1950) Arrhythmias during intracardiac catheterization. Circulation 2:240–244. https://doi.org/10.1161/01.cir.2.2.240
41. Sprung CL, Pozen RG, Rozanski JJ et al (1982) Advanced ventricular arrhythmias during bedside pulmonary artery catheterization. Am J Medicine 72:203–208. https://doi.org/10.1016/0002-9343(82)90811-7
42. Stuart R, Shikora S, Akerman P et al (1990) Incidence of arrhythmia with central venous catheter insertion and exchange. Jpen-parenter Enter 14:152–155. https://doi.org/10.1177/0148607190014002152
43. Haman L, Parizek P, Vojacek J (2009) Precordial thump efficacy in termination of induced ventricular arrhythmias. Resuscitation 80:14–16. https://doi.org/10.1016/j.resuscitation.2008.07.022
44. Pennington JE, Taylor J, Lown B (1970) Chest thump for reverting ventricular tachycardia. New Engl J Medicine 283:1192–1195. https://doi.org/10.1056/nejm197011262832204
45. Levine JH, Guarnieri T, Kadish AH et al (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. https://doi.org/10.1161/01.cir.77.1.70
46. Orini M, Taggart P, Bhuva A et al (2021) Direct in-vivo assessment of global and regional mechano-electric feedback in the intact human heart. Heart Rhythm 18:1406. https://doi.org/10.1016/j.hrthm.2021.04.026
47. Taggart P, Sutton P, Lab M et al (1992) Effect of abrupt changes in ventricular loading on repolarization induced by transient aortic occlusion in humans. Am J Physiology-Heart Circ Physiol 263:H816–H823. https://doi.org/10.1152/ajpheart.1992.263.3.h816
48. Taggart P, Sutton P, John R et al (1992) Monophasic action potential recordings during acute changes in ventricular loading induced by the Valsalva manoeuvre. Brit Heart J 67:221. https://doi.org/10.1136/hrt.67.3.221
49. Taggart P, Sutton P (2011) Load dependence of ventricular repolarization. In: Kohl P, Sachs F, Franz MR (eds) Cardiac Mechano-electric coupling and arrhythmias, 2nd edn. Oxford University Press, Oxford, pp 269–273
50. Sideris DA, Kontoyannis DA, Michalis L et al (1987) Acute changes in blood pressure as a cause of cardiac arrhythmias. Eur Heart J 8:45–52. https://doi.org/10.1093/oxfordjournals.eurheartj.a062158
51. Muller JE, Tofler GH, Stone PH (1989) Circadian variation and triggers of onset of acute cardiovascular disease. Circulation 79:733–743. https://doi.org/10.1161/01.cir.79.4.733

52. Reiter MJ, Stromberg KD, Whitman TA et al (2013) Influence of intracardiac pressure on spontaneous ventricular arrhythmias in patients with systolic heart failure. Circulation Arrhythmia Electrophysiol 6:272–278. https://doi.org/10.1161/circep.113.000223
53. Ambrosi P, Habib G, Kreitmann B et al (1995) Valsalva manoeuvre for supraventricular tachycardia in transplanted heart recipient. Lancet 346:713. https://doi.org/10.1016/s0140-6736(95)92331-4
54. Hwang E-S, Pak H-N (2012) Mid-septal hypertrophy and apical ballooning; potential mechanism of ventricular tachycardia storm in patients with hypertrophic cardiomyopathy. Yonsei Med J 53:221–223. https://doi.org/10.3349/ymj.2012.53.1.221
55. Waxman MB, Wald RW, Finley JP et al (1980) Valsalva termination of ventricular tachycardia. Circulation 62:843–851. https://doi.org/10.1161/01.cir.62.4.843
56. Perticone F, Ceravolo R, Maio R et al (1993) Mechano-electric feedback and ventricular arrhythmias in heart failure. The possible role of permanent cardiac stimulation in preventing ventricular tachycardia. Cardiol Rome Italy 38:247–252
57. Wei JY, Greene HL, Weisfeldt ML (1980) Cough-facilitated conversion of ventricular tachycardia. Am J Cardiol 45:174–176. https://doi.org/10.1016/0002-9149(80)90235-0
58. Nesbitt AD, Cooper PJ, Kohl P (2001) Rediscovering commotio cordis. Lancet 357:1195–1197. https://doi.org/10.1016/s0140-6736(00)04338-5
59. Schlomka G (1934) Ergeb Inn Med Kinderheilkd 47:1–91. https://doi.org/10.1007/978-3-642-90672-5_1
60. Link MS, Wang PJ, Pandian NG et al (1998) An experimental model of sudden death due to low-energy chest-wall impact (commotio cordis). New Engl J Medicine 338:1805–1811. https://doi.org/10.1056/nejm199806183382504
61. Link MS, Maron BJ, VanderBrink BA et al (2001) Impact directly over the cardiac silhouette is necessary to produce ventricular fibrillation in an experimental model of commotio cordis. J Am Coll Cardiol 37:649–654. https://doi.org/10.1016/s0735-1097(00)01142-6
62. Link MS, Maron BJ, Wang PJ et al (2003) Upper and lower limits of vulnerability to sudden arrhythmic death with chest-wall impact (commotio cordis). J Am Coll Cardiol 41:99–104. https://doi.org/10.1016/s0735-1097(02)02669-4
63. Quinn TA, Jin H, Lee P, Kohl P (2017) Mechanically induced ectopy via stretch-activated cation-nonselective channels is caused by local tissue deformation and results in ventricular fibrillation if triggered on the repolarization wave edge (commotio cordis). Circ Arrhythmia Electrophysiol 10:e004777. https://doi.org/10.1161/circep.116.004777
64. Garny A, Kohl P (2004) Mechanical induction of arrhythmias during ventricular repolarization: modeling cellular mechanisms and their interaction in two dimensions. Ann N Y Acad Sci 1015:133–143. https://doi.org/10.1196/annals.1302.011
65. Li W, Kohl P, Trayanova N (2004) Induction of ventricular arrhythmias following mechanical impact: a simulation study in 3D. J Mol Histol 35:679–686. https://doi.org/10.1007/s10735-004-2666-8
66. Alsheikh-Ali AA, Akelman C, Madias C et al (2008) Endocardial mapping of ventricular fibrillation in commotio cordis. Heart Rhythm 5:1355–1356. https://doi.org/10.1016/j.hrthm.2008.03.009
67. Franz MR, Cima R, Wang D et al (1992) Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. Circulation 86:968–978. https://doi.org/10.1161/01.cir.86.3.968
68. Bode F, Franz MR, Wilke I et al (2006) Ventricular fibrillation induced by stretch pulse: implications for sudden death due to commotio cordis. J Cardiovasc Electr 17:1011–1017. https://doi.org/10.1111/j.1540-8167.2006.00547.x
69. Eckardt L, Kirchhof P, Mönnig G et al (2000) Modification of stretch-induced shortening of repolarization by streptomycin in the isolated rabbit heart. J Cardiovasc Pharmacol 36:711–721. https://doi.org/10.1097/00005344-200012000-00005

70. Zabel M, Koller BS, Sachs F et al (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. https://doi.org/10.1016/s0008-6363(96)00089-2
71. Franz MR, Burkhoff D, Yue DT et al (1989) Mechanically induced action potential changes and arrhythmia in isolated and in situ canine hearts. Cardiovasc Res 23:213–223. https://doi.org/10.1093/cvr/23.3.213
72. Hansen DE, Craig CS, Hondeghem LM (1990) Stretch-induced arrhythmias in the isolated canine ventricle. Evidence for the importance of mechanoelectrical feedback. Circulation 81:1094–1105. https://doi.org/10.1161/01.cir.81.3.1094
73. Huang H, Wei H, Liu P et al (2009) A simple automated stimulator of mechanically induced arrhythmias in the isolated rat heart. Exp Physiol 94:1054–1061. https://doi.org/10.1113/expphysiol.2009.048660
74. Kim DY, White E, Saint DA (2012) Increased mechanically-induced ectopy in the hypertrophied heart. Prog Biophysics Mol Biol 110:331–339. https://doi.org/10.1016/j.pbiomolbio.2012.07.004
75. Dhein S, Englert C, Riethdorf S et al (2014) Arrhythmogenic effects by local left ventricular stretch: effects of flecainide and streptomycin. N-S Arch Pharmacol 387:763–775. https://doi.org/10.1007/s00210-014-0988-y
76. Wei H, Zhang Z-F, Huang H-X, Niu W-Z (2008) [Arrhythmia triggered by stretching rabbit left ventricles and the block effect of streptomycin] Zhongguo Ying Yong Sheng Li Xue Za Zhi Zhongguo Yingyong Shenglixue Zazhi Chin. J Appl Physiol 24:286–289
77. Dick DJ, Lab MJ (1998) Mechanical modulation of stretch-induced premature ventricular beats: induction of a mechanoelectric adaptation period. Cardiovasc Res 38:181–191. https://doi.org/10.1016/s0008-6363(97)00314-3
78. Hansen DE, Borganelli M, Stacy GP Jr et al (1991) Dose-dependent inhibition of stretch-induced arrhythmias by gadolinium in isolated canine ventricles. Evidence for a unique mode of antiarrhythmic action. Circ Res 69:820–831. https://doi.org/10.1161/01.res.69.3.820
79. Nazir SA, Lab MJ (1996) Mechanoelectric feedback in the atrium of the isolated Guinea-pig heart. Cardiovasc Res 32:112–119
80. Parker KK, Lavelle JA, Taylor LK et al (2004) Stretch-induced ventricular arrhythmias during acute ischemia and reperfusion. J Appl Physiol 97:377–383. https://doi.org/10.1152/japplphysiol.01235.2001
81. Parker KK, Taylor LK, Atkinson JB et al (2001) The effects of tubulin-binding agents on stretch-induced ventricular arrhythmias. Eur J Pharmacol 417:131–140. https://doi.org/10.1016/s0014-2999(01)00856-1
82. Reiter MJ, Synhorst DP, Mann DE (1988) Electrophysiological effects of acute ventricular dilatation in the isolated rabbit heart. Circ Res 62:554–562. https://doi.org/10.1161/01.res.62.3.554
83. Seo K, Inagaki M, Nishimura S et al (2010) Structural heterogeneity in the ventricular wall plays a significant role in the initiation of stretch-induced arrhythmias in perfused rabbit right ventricular tissues and whole heart preparations. Circ Res 106:176–184. https://doi.org/10.1161/circresaha.109.203828
84. Stacy GP, Jobe RL, Taylor LK et al (1992) Stretch-induced depolarizations as a trigger of arrhythmias in isolated canine left ventricles. Am J Physiology-Heart Circ Physiol 263:H613–H621. https://doi.org/10.1152/ajpheart.1992.263.2.h613
85. Sideris DA, Chrysos DN, Maliaras GK et al (1988) Effect of acute hypertension on the cardiac rhythm. Experimental observations J Electrocardiol 21:183–191. https://doi.org/10.1016/s0022-0736(88)80015-3
86. Sideris DA, Toumanidis ST, Kostis EB et al (1989) Arrhythmogenic effect of high blood pressure: some observations on its mechanism. Cardiovasc Res 23:983–992. https://doi.org/10.1093/cvr/23.11.983
87. Sideris DA, Toumanidis ST, Kostis EB et al (1991) Effect of adrenergic blockade on pressure-related ventricular arrhythmias. Acta Cardiol 46:215–225

88. Haemers P, Sutherland G, Cikes M et al (2015) Further insights into blood pressure induced premature beats: transient depolarizations are associated with fast myocardial deformation upon pressure decline. Heart Rhythm 12:2305–2315. https://doi.org/10.1016/j.hrthm.2015.06.037
89. Calkins H, Maughan WL, Weisman HF et al (1989) Effect of acute volume load on refractoriness and arrhythmia development in isolated, chronically infarcted canine hearts. Circulation 79:687–697. https://doi.org/10.1161/01.cir.79.3.687
90. Chen RL, Penny DJ, Greve G et al (2004) Stretch-induced regional mechanoelectric dispersion and arrhythmia in the right ventricle of anesthetized lambs. Am J Physiology Hear Circ Physiol 286:H1008–H1014. https://doi.org/10.1152/ajpheart.00724.2003
91. Zabel M, Portnoy S, Franz MR (1996) Effect of sustained load on dispersion of ventricular repolarization and conduction time in the isolated intact rabbit heart. J Cardiovasc Electr 7:9–16. https://doi.org/10.1111/j.1540-8167.1996.tb00455.x
92. Belus A, White E (2003) Streptomycin and intracellular calcium modulate the response of single Guinea-pig ventricular myocytes to axial stretch. J Physiol 546:501–509. https://doi.org/10.1113/jphysiol.2002.027573
93. Benditt DG, Kriett JM, Tobler HG et al (1985) Electrophysiological effects of transient aortic occlusion in intact canine heart. Am J Physiology-Heart Circ Physiol 249:H1017–H1023. https://doi.org/10.1152/ajpheart.1985.249.5.h1017
94. Burton FL, Cobbe SM (1998) Effect of sustained stretch on dispersion of ventricular fibrillation intervals in normal rabbit hearts. Cardiovasc Res 39:351–359. https://doi.org/10.1016/s0008-6363(98)00092-3
95. Calkins H, Levine JH, Kass DA (1991) Electrophysiological effect of varied rate and extent of acute in vivo left ventricular load increase. Cardiovasc Res 25:637–644. https://doi.org/10.1093/cvr/25.8.637
96. Coulshed DS, Cowan JC (1991) Contraction-excitation feedback in an ejecting whole heart model – dependence of action potential duration on left ventricular diastolic and systolic pressures. Cardiovasc Res 25:343–352. https://doi.org/10.1093/cvr/25.4.343
97. Coulshed DS, Cowan JC, Drinkhill MJ et al (1992) The effects of ventricular end-diastolic and systolic pressures on action potential and duration in anaesthetized dogs. J Physiol 457:75–91. https://doi.org/10.1113/jphysiol.1992.sp019365
98. Coulshed DS, Hainsworth R, Cowan JC (1994) The influence of myocardial systolic shortening on action potential duration following changes in left ventricular end-diastolic pressure. J Cardiovasc Electr 5:919–932. https://doi.org/10.1111/j.1540-8167.1994.tb01132.x
99. Dean JW, Lab MJ (1989) Effect of changes in load on monophasic action potential and segment length of pig heart in situ. Cardiovasc Res 23:887–887. https://doi.org/10.1093/cvr/23.10.887
100. Dean JW, Lab MJ (1990) Regional changes in ventricular excitability during load manipulation of the in situ pig heart. J Physiology 429:387–400. https://doi.org/10.1113/jphysiol.1990.sp018263
101. Greve G, Lab MJ, Chen R et al (2001) Right ventricular distension alters monophasic action potential duration during pulmonary arterial occlusion in anaesthetised lambs: evidence for arrhythmogenic right ventricular mechanoelectrical feedback. Exp Physiol 86:651–657. https://doi.org/10.1113/eph8602225
102. Halperin BD, Adler SW, Mann DE et al (1993) Mechanical correlates of contraction-excitation feedback during acute ventricular dilatation. Cardiovasc Res 27:1084–1087. https://doi.org/10.1093/cvr/27.6.1084
103. Horner SM, Dick DJ, Murphy CF et al (1996) Cycle length dependence of the electrophysiological effects of increased load on the myocardium. Circulation 94:1131–1136. https://doi.org/10.1161/01.cir.94.5.1131
104. Lab MJ (1980) Transient depolarisation and action potential alterations following mechanical changes in isolated myocardium. Cardiovasc Res 14:624–637. https://doi.org/10.1093/cvr/14.11.624

105. Lerman BB, Burkhoff D, Yue DT et al (1985) Mechanoelectrical feedback: independent role of preload and contractility in modulation of canine ventricular excitability. J Clin Invest 76: 1843–1850. https://doi.org/10.1172/jci112177
106. Reiter MJ, Zetelaki Z, Kirchhof CJ et al (1994) Interaction of acute ventricular dilatation and d-sotalol during sustained reentrant ventricular tachycardia around a fixed obstacle. Circulation 89:423–431. https://doi.org/10.1161/01.cir.89.1.423
107. Reiter MJ, Landers M, Zetelaki Z et al (1997) Electrophysiological effects of acute dilatation in the isolated rabbit heart: cycle length–dependent effects on ventricular refractoriness and conduction velocity. Circulation 96:4050–4056. https://doi.org/10.1161/01.cir.96.11.4050
108. Sung D, Mills RW, Schettler J et al (2003) Ventricular filling slows epicardial conduction and increases action potential duration in an optical mapping study of the isolated rabbit heart. J Cardiovasc Electr 14:739–749. https://doi.org/10.1046/j.1540-8167.2003.03072.x
109. Wang K, Terrar D, Gavaghan DJ et al (2014) Living cardiac tissue slices: an organotypic pseudo two-dimensional model for cardiac biophysics research. Prog Biophysics Mol Biology 115:314–327. https://doi.org/10.1016/j.pbiomolbio.2014.08.006
110. Wang X-X, Cheng L-X, Chen J-Z et al (2003) Dependence of ventricular wall stress-induced refractoriness changes on pacing cycle lengths and its mechanism. Sheng Li Xue Bao Acta Physiologica Sinica 55:336–338
111. Werdich AA, Brzezinski A, Jeyaraj D et al (2012) The zebrafish as a novel animal model to study the molecular mechanisms of mechano-electrical feedback in the heart. Prog Biophysics Mol Biology 110:154–165. https://doi.org/10.1016/j.pbiomolbio.2012.07.006
112. Quintanilla JG, Moreno J, Archondo T et al (2015) Increased intraventricular pressures are as harmful as the electrophysiological substrate of heart failure in favoring sustained reentry in the swine heart. Heart Rhythm 12:2172–2183. https://doi.org/10.1016/j.hrthm.2015.05.017
113. Quinn TA (2014) The importance of non-uniformities in mechano-electric coupling for ventricular arrhythmias. J Interv Card Electr 39:25–35. https://doi.org/10.1007/s10840-013-9852-0
114. Caporizzo MA, Chen CY, Prosser BL (2019) Cardiac microtubules in health and heart disease. Exp Biol Med 244:1255–1272. https://doi.org/10.1177/1535370219868960
115. Kerr JP, Robison P, Shi G et al (2015) Detyrosinated microtubules modulate mechanotransduction in heart and skeletal muscle. Nat Commun 6:8526. https://doi.org/10.1038/ncomms9526
116. Robison P, Prosser BL (2017) Microtubule mechanics in the working myocyte. J Physiol 595: 3931–3937. https://doi.org/10.1113/jp273046
117. Chen-Izu Y, Izu LT (2017) Mechano-chemo-transduction in cardiac myocytes. J Physiol 595: 3949–3958. https://doi.org/10.1113/jp273101
118. Iribe G, Ward CW, Camelliti P et al (2009) Axial stretch of rat single ventricular cardiomyocytes causes an acute and transient increase in Ca^{2+} spark rate. Circ Res 104:787–795. https://doi.org/10.1161/circresaha.108.193334
119. Izu LT, Kohl P, Boyden PA et al (2020) Mechano-electric and mechano-chemo-transduction in cardiomyocytes. J Physiol 598:1285–1305. https://doi.org/10.1113/jp276494
120. Prosser BL, Ward CW, Lederer WJ (2011) X-ROS signaling: rapid mechano-chemo transduction in heart. Science 333:1440–1445. https://doi.org/10.1126/science.1202768
121. Prosser BL, Ward CW (2014) Mechano-chemo transduction tunes the heartstrings. Sci Signal 7:pe7. https://doi.org/10.1126/scisignal.2005214
122. Kohl P, Bollensdorff C, Garny A (2006) Effects of mechanosensitive ion channels on ventricular electrophysiology: experimental and theoretical models. Exp Physiol 91:307–321. https://doi.org/10.1113/expphysiol.2005.031062
123. Morris CE (2011) Pacemaker, potassium, calcium, sodium: stretch modulation of the voltage-gated channels. In: Kohl P, Sachs F, Franz MR (eds) Cardiac Mechano-electric coupling and arrhythmias, 2nd edn. Oxford University Press, Oxford, pp 42–49
124. Vandenberg JI, Rees SA, Wright AR et al (1996) Cell swelling and ion transport pathways in cardiac myocytes. Cardiovasc Res 32:85–97. https://doi.org/10.1016/s0008-6363(96)00048-x

125. Baumgarten CM, Clemo HF (2003) Swelling-activated chloride channels in cardiac physiology and pathophysiology. Prog Biophysics Mol Biology 82:25–42. https://doi.org/10.1016/s0079-6107(03)00003-8
126. Craelius W (1993) Stretch-activation of rat cardiac myocytes. Exp Physiol 78:411–423. https://doi.org/10.1113/expphysiol.1993.sp003695
127. Riemer TL, Tung L (2003) Stretch-induced excitation and action potential changes of single cardiac cells. Prog Biophysics Mol Biology 82:97–110. https://doi.org/10.1016/s0079-6107(03)00008-7
128. Gannier F, White E, Lacampagne A et al (1994) Streptomycin reverses a large stretch induced increase in $[Ca^{2+}]_i$ in isolated Guinea pig ventricular myocytes. Cardiovasc Res 28:1193–1198. https://doi.org/10.1093/cvr/28.8.1193
129. Smani T, Dionisio N, López JJ et al (2014) Cytoskeletal and scaffolding proteins as structural and functional determinants of TRP channels. Biochimica Et Biophysica Acta Bba - Biomembr 1838:658–664. https://doi.org/10.1016/j.bbamem.2013.01.009
130. Coste B, Mathur J, Schmidt M et al (2010) Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. Science 330:55–60. https://doi.org/10.1126/science.1193270
131. Volkers L, Mechioukhi Y, Coste B (2015) Piezo channels: from structure to function. Pflügers Archiv - European J Physiol 467:95–99. https://doi.org/10.1007/s00424-014-1578-z
132. Solis AG, Bielecki P, Steach HR et al (2019) Mechanosensation of cyclical force by PIEZO1 is essential for innate immunity. Nature 573:69–74. https://doi.org/10.1038/s41586-019-1485-8
133. Blythe NM, Muraki K, Ludlow MJ et al (2019) Mechanically activated Piezo1 channels of cardiac fibroblasts stimulate p38 mitogen-activated protein kinase activity and interleukin-6 secretion. J Biol Chem 294:17395–17408. https://doi.org/10.1074/jbc.ra119.009167
134. Cameron BA, Stoyek MR, Bak JJ et al (n.d.) TRPA1 channels are a source of calcium-driven cardiac mechano-arrhythmogenicity. bioRxiv. https://doi.org/10.1101/2020.10.01.321638
135. Watanabe H, Murakami M, Ohba T et al (2008) TRP channel and cardiovascular disease. Pharmacol Therapeut 118:337–351. https://doi.org/10.1016/j.pharmthera.2008.03.008
136. Inoue R, Jian Z, Kawarabayashi Y (2009) Mechanosensitive TRP channels in cardiovascular pathophysiology. Pharmacol Therapeut 123:371–385. https://doi.org/10.1016/j.pharmthera.2009.05.009
137. Nikolaev YA, Cox CD, Ridone P et al (2019) Mammalian TRP ion channels are insensitive to membrane stretch. J Cell Sci 132:jcs238360. https://doi.org/10.1242/jcs.238360
138. Li W, Kohl P, Trayanova N (2006) Myocardial ischemia lowers precordial thump efficacy: an inquiry into mechanisms using three-dimensional simulations. Heart Rhythm 3:179–186. https://doi.org/10.1016/j.hrthm.2005.10.033
139. Wagoner DRV, Lamorgese M (1994) Ischemia potentiates the mechanosensitive modulation of atrial ATP-sensitive potassium channels. Ann N Y Acad Sci 723:392–395. https://doi.org/10.1111/j.1749-6632.1994.tb36755.x
140. Wagoner DRV (1993) Mechanosensitive gating of atrial ATP-sensitive potassium channels. Circ Res 72:973–983. https://doi.org/10.1161/01.res.72.5.973
141. Rog-Zielinska EA, O'Toole ET, Hoenger A et al (2019) Mitochondrial deformation during the cardiac mechanical cycle. Anatomical Rec 302:146–152. https://doi.org/10.1002/ar.23917
142. Belmonte S, Morad M (2008) 'Pressure–flow'-triggered intracellular Ca^{2+} transients in rat cardiac myocytes: possible mechanisms and role of mitochondria. J Physiol 586:1379–1397. https://doi.org/10.1113/jphysiol.2007.149294
143. Belmonte S, Morad M (2008) Shear fluid-induced Ca^{2+} release and the role of mitochondria in rat cardiac myocytes. Ann N Y Acad Sci 1123:58–63. https://doi.org/10.1196/annals.1420.007
144. Miragoli M, Sanchez-Alonso JL, Bhargava A et al (2015) Microtubule-dependent mitochondria alignment regulates calcium release in response to nanomechanical stimulus in heart myocytes. Cell Rep 14:140–151. https://doi.org/10.1016/j.celrep.2015.12.014

145. Morad M, Javaheri A, Risius T et al (2005) Multimodality of Ca^{2+} signaling in rat atrial myocytes. Ann N Y Acad Sci 1047:112–121. https://doi.org/10.1196/annals.1341.010
146. Janke C, Bulinski JC (2011) Post-translational regulation of the microtubule cytoskeleton: mechanisms and functions. Nat Rev Mol Cell Bio 12:773–786. https://doi.org/10.1038/nrm3227
147. Portran D, Schaedel L, Xu Z et al (2017) Tubulin acetylation protects long-lived microtubules against mechanical ageing. Nat Cell Biol 19:391–398. https://doi.org/10.1038/ncb3481
148. Hirata H, Tatsumi H, Hayakawa K et al (2015) Non-channel mechanosensors working at focal adhesion-stress fiber complex. Pflügers Archiv - European J Physiol 467:141–155. https://doi.org/10.1007/s00424-014-1558-3
149. Israeli-Rosenberg S, Chen C, Li R et al (2015) Caveolin modulates integrin function and mechanical activation in the cardiomyocyte. FASEB J 29:374–384. https://doi.org/10.1096/fj.13-243139
150. Robison P, Caporizzo MA, Ahmadzadeh H et al (2016) Detyrosinated microtubules buckle and bear load in contracting cardiomyocytes. Science 352:aaf0659. https://doi.org/10.1126/science.aaf0659
151. Brangwynne CP, MacKintosh FC, Kumar S et al (2006) Microtubules can bear enhanced compressive loads in living cells because of lateral reinforcement. J Cell Biol 173:733–741. https://doi.org/10.1083/jcb.200601060
152. Salomon AK, Okami N, Heffler J et al (2021) Desmin intermediate filaments and tubulin detyrosination stabilize growing microtubules in the cardiomyocyte bioRxiv 2021.05.26.445641. https://doi.org/10.1101/2021.05.26.445641
153. Belmadani S, Poüs C, Ventura-Clapier R et al (2002) Post-translational modifications of cardiac tubulin during chronic heart failure in the rat. Mol Cell Biochem 237:39–46. https://doi.org/10.1023/a:1016554104209
154. Xu Z, Schaedel L, Portran D et al (2017) Microtubules acquire resistance from mechanical breakage through intralumenal acetylation. Science 356:328–332. https://doi.org/10.1126/science.aai8764
155. Coleman AK, Joca HC, Shi G et al (2021) Tubulin acetylation increases cytoskeletal stiffness to regulate mechanotransduction in striated muscle. J Gen Physiol 153:e202012743. https://doi.org/10.1085/jgp.202012743
156. ter Keurs HEDJ, Boyden PA (2007) Calcium and arrhythmogenesis. Physiol Rev 87:457–506. https://doi.org/10.1152/physrev.00011.2006
157. Landstrom AP, Dobrev D, Wehrens XHT (2017) Calcium signaling and cardiac arrhythmias. Circ Res 120:1969–1993. https://doi.org/10.1161/circresaha.117.310083
158. Iribe G, Kohl P (2008) Axial stretch enhances sarcoplasmic reticulum Ca^{2+} leak and cellular Ca^{2+} reuptake in Guinea pig ventricular myocytes: experiments and models. Prog Biophysics Mol Biology 97:298–311. https://doi.org/10.1016/j.pbiomolbio.2008.02.012
159. Schönleitner P, Schotten U, Antoons G (2017) Mechanosensitivity of microdomain calcium signalling in the heart. Prog Biophysics Mol Biology 130:288–301. https://doi.org/10.1016/j.pbiomolbio.2017.06.013
160. Allen DG, Kentish JC (1988) Calcium concentration in the myoplasm of skinned ferret ventricular muscle following changes in muscle length. J Physiol 407:489–503. https://doi.org/10.1113/jphysiol.1988.sp017427
161. Wakayama Y, Miura M, Stuyvers BD et al (2005) Spatial nonuniformity of excitation–contraction coupling causes arrhythmogenic Ca^{2+}; waves in rat cardiac muscle. Circ Res 96:1266–1273. https://doi.org/10.1161/01.res.0000172544.56818.54
162. Andersson DA, Gentry C, Moss S et al (2008) Transient receptor potential A1 is a sensory receptor for multiple products of oxidative stress. J Neurosci 28:2485–2494. https://doi.org/10.1523/jneurosci.5369-07.2008
163. Zurborg S, Yurgionas B, Jira JA et al (2007) Direct activation of the ion channel TRPA1 by Ca^{2+}. Nat Neurosci 10:277–279. https://doi.org/10.1038/nn1843

164. Iribe G, Jin H, Kaihara K et al (2010) Effects of axial stretch on sarcolemmal BKCa channels in post-hatch chick ventricular myocytes. Exp Physiol 95:699–711. https://doi.org/10.1113/expphysiol.2009.051896
165. Goldblum RR, McClellan M, White K et al (2021) Oxidative stress pathogenically remodels the cardiac myocyte cytoskeleton via structural alterations to the microtubule lattice. Dev Cell 56:2252. https://doi.org/10.1016/j.devcel.2021.07.004
166. Cannell MB (2009) Pulling on the heart strings: a new mechanism within Starling's law of the heart? Circ Res 104:715–716. https://doi.org/10.1161/circresaha.109.195511
167. Belevych AE, Terentyev D, Viatchenko-Karpinski S et al (2009) Redox modification of ryanodine receptors underlies calcium alternans in a canine model of sudden cardiac death. Cardiovasc Res 84:387–395. https://doi.org/10.1093/cvr/cvp246
168. Prosser BL, Ward CW, Lederer WJ (2010) Subcellular Ca^{2+} signaling in the heart: the role of ryanodine receptor sensitivity. J Gen Physiology 136:135–142. https://doi.org/10.1085/jgp.201010406
169. Prosser BL, Khairallah RJ, Ziman AP et al (2013) X-ROS signaling in the heart and skeletal muscle: stretch-dependent local ROS regulates $[Ca^{2+}]_i$. J Mol Cell Cardiol 58:172–181. https://doi.org/10.1016/j.yjmcc.2012.11.011
170. Huke S, Knollmann BC (2010) Increased myofilament Ca^{2+}-sensitivity and arrhythmia susceptibility. J Mol Cell Cardiol 48:824–833. https://doi.org/10.1016/j.yjmcc.2010.01.011
171. ter Keurs HEDJ, Shinozaki T, Zhang YM et al (2008) Sarcomere mechanics in uniform and non-uniform cardiac muscle: a link between pump function and arrhythmias. Prog Biophysics Mol Biology 97:312–331. https://doi.org/10.1016/j.pbiomolbio.2008.02.013
172. Cameron BA, Kai H, Kaihara K et al (2020) Ischemia enhances the acute stretch-induced increase in calcium spark rate in ventricular myocytes. Front Physiol 11:289. https://doi.org/10.3389/fphys.2020.00289
173. Prosser BL, Ward CW, Lederer WJ (2013) X-ROS signalling is enhanced and graded by cyclic cardiomyocyte stretch. Cardiovasc Res 98:307–314. https://doi.org/10.1093/cvr/cvt066
174. Solovyova O, Katsnelson LB, Konovalov PV et al (2014) The cardiac muscle duplex as a method to study myocardial heterogeneity. Prog Biophysics Mol Biology 115:115–128. https://doi.org/10.1016/j.pbiomolbio.2014.07.010
175. Tyberg JV, Parmley WW, Sonnenblick EH (1969) In-vitro studies of myocardial asynchrony and regional hypoxia. Circ Res 25:569–579. https://doi.org/10.1161/01.res.25.5.569
176. Carmeliet E (1999) Cardiac ionic currents and acute ischemia: from channels to arrhythmias. Physiol Rev 79:917–1017. https://doi.org/10.1152/physrev.1999.79.3.917
177. Bollensdorff C, Lab M (2011) Stretch effects on potassium accumulation and alternans in pathological myocardium. In: Kohl P, Sachs F, Franz MR (eds) Cardiac Mechano-electric coupling and arrhythmias, 2nd edn. Oxford University Press, Oxford, pp 173–179
178. Janse MJ, Wit AL (1989) Electrophysiological mechanisms of ventricular arrhythmias resulting from myocardial ischemia and infarction. Physiol Rev 69:1049–1169. https://doi.org/10.1152/physrev.1989.69.4.1049
179. Gallagher KP, Gerren RA, Choy M et al (1987) Subendocardial segment length shortening at lateral margins of ischemic myocardium in dogs. Am J Physiology-Heart Circ Physiol 253:H826–H837. https://doi.org/10.1152/ajpheart.1987.253.4.h826
180. Leuven SLV, Waldman LK, McCulloch AD et al (1994) Gradients of epicardial strain across the perfusion boundary during acute myocardial ischemia. Am J Physiology-Heart Circ Physiol 267:H2348–H2362. https://doi.org/10.1152/ajpheart.1994.267.6.h2348
181. Prinzen FW, Arts T, Hoeks APG et al (1989) Discrepancies between myocardial blood flow and fiber shortening in the ischemic border zone as assessed with video mapping of epicardial deformation. Pflugers Arch 415:220–229. https://doi.org/10.1007/bf00370596
182. Sakai K, Watanabe K, Millard RW (1985) Defining the mechanical border zone: a study in the pig heart. Am J Physiology-Heart Circ Physiol 249:H88–H94. https://doi.org/10.1152/ajpheart.1985.249.1.h88

183. Theroux P, Franklin D, Ross J et al (1974) Regional myocardial function during acute coronary artery occlusion and its modification by pharmacologic agents in the dog. Circ Res 35:896–908. https://doi.org/10.1161/01.res.35.6.896
184. Lopaschuk GD, Ussher JR, Folmes CDL et al (2010) Myocardial fatty acid metabolism in health and disease. Physiol Rev 90:207–258. https://doi.org/10.1152/physrev.00015.2009
185. Stanley WC (2001) Changes in cardiac metabolism: a critical step from stable angina to ischaemic cardiomyopathy. Eur Heart J Suppl 3:O2–O7. https://doi.org/10.1016/s1520-765x(01)90147-6
186. Bittl JA, Weisfeldt ML, Jacobus WE (1985) Creatine kinase of heart mitochondria. The progressive loss of enzyme activity during in vivo ischemia and its correlation to depressed myocardial function. J Biol Chem 260:208–214
187. Califf RM, Abdelmeguid AE, Kuntz RE et al (1998) Myonecrosis after revascularization procedures. J Am Coll Cardiol 31:241–251. https://doi.org/10.1016/s0735-1097(97)00506-8
188. Cao F, Zervou S, Lygate CA (2018) The creatine kinase system as a therapeutic target for myocardial ischaemia–reperfusion injury. Biochem Soc T 46:1119–1127. https://doi.org/10.1042/bst20170504
189. Lygate CA, Bohl S, ten Hove M et al (2012) Moderate elevation of intracellular creatine by targeting the creatine transporter protects mice from acute myocardial infarction. Cardiovasc Res 96:466–475. https://doi.org/10.1093/cvr/cvs272
190. Takahashi M, Yokoshiki H, Mitsuyama H et al (2021) SK channel blockade prevents hypoxia-induced ventricular arrhythmias through inhibition of Ca^{2+}/voltage uncoupling in hypertrophied hearts. Am J Physiology-Heart Circ Physiol 320:H1456–H1469. https://doi.org/10.1152/ajpheart.00777.2020
191. Lang D, Holzem K, Kang C et al (2015) Arrhythmogenic remodeling of β2 versus β1 adrenergic signaling in the human failing heart. Circ Arrhythmia Electrophysiol 8:409–419. https://doi.org/10.1161/circep.114.002065
192. Tang L, Joung B, Ogawa M et al (2012) Intracellular calcium dynamics, shortened action potential duration, and late-phase 3 early afterdepolarization in Langendorff-perfused rabbit ventricles. J Cardiovasc Electr 23:1364–1371. https://doi.org/10.1111/j.1540-8167.2012.02400.x
193. Michailova A, Lorentz W, McCulloch A (2007) Modeling transmural heterogeneity of K_{ATP} current in rabbit ventricular myocytes. Am J Physiol-Cell Ph 293:C542–C557. https://doi.org/10.1152/ajpcell.00148.2006
194. Baumeister P, Quinn TA (2016) Altered calcium handling and ventricular arrhythmias in acute ischemia. Clin Medicine Insights Cardiol 10s1:61–69. https://doi.org/10.4137/cmc.s39706
195. Coronel R, Fiolet JW, Wilms-Schopman FJ et al (1988) Distribution of extracellular potassium and its relation to electrophysiologic changes during acute myocardial ischemia in the isolated perfused porcine heart. Circulation 77:1125–1138. https://doi.org/10.1161/01.cir.77.5.1125
196. Coronel R, Wilms-Schopman FJ, Opthof T et al (1991) Injury current and gradients of diastolic stimulation threshold, TQ potential, and extracellular potassium concentration during acute regional ischemia in the isolated perfused pig heart. Circ Res 68:1241–1249. https://doi.org/10.1161/01.res.68.5.1241
197. de Groot JR, Coronel R (2004) Acute ischemia-induced gap junctional uncoupling and arrhythmogenesis. Cardiovasc Res 62:323–334. https://doi.org/10.1016/j.cardiores.2004.01.033
198. Dries E, Amoni M, Vandenberk B et al (2020) Altered adrenergic response in myocytes bordering a chronic myocardial infarction underlies in vivo triggered activity and repolarization instability. J Physiology 598:2875–2895. https://doi.org/10.1113/jp278839
199. Mills RW, Narayan SM, McCulloch AD (2008) Mechanisms of conduction slowing during myocardial stretch by ventricular volume loading in the rabbit. Am J Physiology-Heart Circ Physiol 295:H1270–H1278. https://doi.org/10.1152/ajpheart.00350.2008

200. de Oliveira BL, Pfeiffer ER, Sundnes J et al (2015) Increased cell membrane capacitance is the dominant mechanism of stretch-dependent conduction slowing in the rabbit heart: a computational study. Cell Mol Bioeng 8:237–246. https://doi.org/10.1007/s12195-015-0384-9
201. Kohl P, Cooper PJ, Holloway H (2003) Effects of acute ventricular volume manipulation on in situ cardiomyocyte cell membrane configuration. Prog Biophysics Mol Biology 82:221–227. https://doi.org/10.1016/s0079-6107(03)00024-5
202. Rog-Zielinska EA, Scardigli M, Peyronnet R et al (2021) Beat-by-beat cardiomyocyte T-tubule deformation drives tubular content exchange. Circ Res 128:203–215. https://doi.org/10.1161/circresaha.120.317266
203. Cannell M, Cheng H, Lederer W (1995) The control of calcium release in heart muscle. Science 268:1045–1049. https://doi.org/10.1126/science.7754384
204. Hj H, Hoeher M, Risse JH (1987) Cardiac energetics, basic mechanisms and clinical implications. Basic Res Cardiol 82(Suppl 2):301–310. https://doi.org/10.1007/978-3-662-11289-2_29
205. Jie X, Gurev V, Trayanova N (2010) Mechanisms of mechanically induced spontaneous arrhythmias in acute regional ischemia. Circ Res 106:185–192. https://doi.org/10.1161/circresaha.109.210864
206. Limbu S, Hoang-Trong TM, Prosser BL et al (2015) Modeling local X-ROS and calcium signaling in the heart. Biophys J 109:2037–2050. https://doi.org/10.1016/j.bpj.2015.09.031
207. Ferrari R, Ceconi C, Curello S et al (1985) Oxygen-mediated myocardial damage during ischaemia and reperfusion: role of the cellular defences against oxygen toxicity. J Mol Cell Cardiol 17:937–945. https://doi.org/10.1016/s0022-2828(85)80074-2
208. Miura M, Taguchi Y, Handoh T et al (2018) Regional increase in ROS within stretched region exacerbates arrhythmias in rat trabeculae with nonuniform contraction. Pflügers Archiv - European J Physiol 470:1349–1357. https://doi.org/10.1007/s00424-018-2152-x
209. Meents JE, Fischer MJM, McNaughton PA (2016) Agonist-induced sensitisation of the irritant receptor ion channel TRPA1. J Physiology 594:6643–6660. https://doi.org/10.1113/jp272237
210. Tan JHC, Liu W, Saint DA (2004) Differential expression of the mechanosensitive potassium channel TREK-1 in epicardial and endocardial myocytes in rat ventricle. Exp Physiol 89:237–242. https://doi.org/10.1113/expphysiol.2003.027052
211. Coronel R, Wilms-Schopman FJG, Opthof T et al (2009) Dispersion of repolarization and arrhythmogenesis. Heart Rhythm 6:537–543. https://doi.org/10.1016/j.hrthm.2009.01.013
212. Whelton PK, Carey RM, Aronow WS et al (2018) 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults. Hypertension 71:e13–e115. https://doi.org/10.1161/hyp.0000000000000065
213. Frohlich ED, Susic D (2012) Pressure overload. Heart Fail Clin 8:21–32. https://doi.org/10.1016/j.hfc.2011.08.005
214. Konstam MA, Kramer DG, Patel AR et al (2011) Left ventricular remodeling in heart failure current concepts in clinical significance and assessment. JACC Cardiovasc Imaging 4:98–108. https://doi.org/10.1016/j.jcmg.2010.10.008
215. Lorell BH, Carabello BA (2000) Left ventricular hypertrophy. Circulation 102:470–479. https://doi.org/10.1161/01.cir.102.4.470
216. Kahan T, Bergfeldt L (2005) Left ventricular hypertrophy in hypertension: its arrhythmogenic potential. Heart 91:250. https://doi.org/10.1136/hrt.2004.042473
217. McLenachan JM, Henderson E, Morris KI et al (1987) Ventricular arrhythmias in patients with hypertensive left ventricular hypertrophy. New Engl J Medicine 317:787–792. https://doi.org/10.1056/nejm198709243171302
218. Rapsomaniki E, Timmis A, George J et al (2014) Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. Lancet 383:1899–1911. https://doi.org/10.1016/s0140-6736(14)60685-1
219. Shenasa M, Shenasa H (2017) Hypertension, left ventricular hypertrophy, and sudden cardiac death. Int J Cardiol 237:60–63. https://doi.org/10.1016/j.ijcard.2017.03.002

220. Tereshchenko LG, Soliman EZ, Davis BR et al (2017) Risk stratification of sudden cardiac death in hypertension. J Electrocardiol 50:798–801. https://doi.org/10.1016/j.jelectrocard.2017.08.012
221. Yiu K-H, Tse H-F (2008) Hypertension and cardiac arrhythmias: a review of the epidemiology, pathophysiology and clinical implications. J Hum Hypertens 22:380–388. https://doi.org/10.1038/jhh.2008.10
222. Dunn FG, Pringle SD (1987) Left ventricular hypertrophy and myocardial ischemia in systemic hypertension. Am J Cardiol 60:19–22. https://doi.org/10.1016/0002-9149(87)90454-1
223. Katz AM (2002) Ernest Henry Starling, his predecessors, and the "Law of the Heart.". Circulation 106:2986–2992. https://doi.org/10.1161/01.cir.0000040594.96123.55
224. Maliken BD, Molkentin JD (2018) Undeniable evidence that the adult mammalian heart lacks an endogenous regenerative stem cell. Circulation 138:806–808. https://doi.org/10.1161/circulationaha.118.035186
225. Cooper G (2000) Cardiocyte cytoskeleton in hypertrophied myocardium. Heart Fail Rev 5:187–201. https://doi.org/10.1023/a:1009836918377
226. ter Keurs HEDJ (1998) Microtubules in cardiac hypertrophy. Circ Res 82:828–831. https://doi.org/10.1161/01.res.82.7.828
227. Caporizzo MA, Chen CY, Bedi K et al (2020) Microtubules increase diastolic stiffness in failing human cardiomyocytes and myocardium. Circulation 141:902–915. https://doi.org/10.1161/circulationaha.119.043930
228. Chen CY, Caporizzo MA, Bedi K et al (2018) Suppression of detyrosinated microtubules improves cardiomyocyte function in human heart failure. Nat Med 24:1225–1233. https://doi.org/10.1038/s41591-018-0046-2
229. Tagawa H, Wang N, Narishige T et al (1997) Cytoskeletal mechanics in pressure-overload cardiac hypertrophy. Circ Res 80:281–289. https://doi.org/10.1161/01.res.80.2.281
230. Yamamoto S, Tsutsui H, Takahashi M et al (1998) Role of microtubules in the viscoelastic properties of isolated cardiac muscle. J Mol Cell Cardiol 30:1841–1853. https://doi.org/10.1006/jmcc.1998.0747
231. Tagawa H, Koide M, Sato H et al (1998) Cytoskeletal role in the transition from compensated to decompensated hypertrophy during adult canine left ventricular pressure overloading. Circ Res 82:751–761. https://doi.org/10.1161/01.res.82.7.751
232. Nishimura S, Nagai S, Katoh M et al (2006) Microtubules modulate the stiffness of cardiomyocytes against shear stress. Circ Res 98:81–87. https://doi.org/10.1161/01.res.0000197785.51819.e8
233. Zile MR, Richardson K, Cowles MK et al (1998) Constitutive properties of adult mammalian cardiac muscle cells. Circulation 98:567–579. https://doi.org/10.1161/01.cir.98.6.567
234. Koide M, Hamawaki M, Narishige T et al (2000) Microtubule depolymerization normalizes in vivo myocardial contractile function in dogs with pressure-overload left ventricular hypertrophy. Circulation 102:1045–1052. https://doi.org/10.1161/01.cir.102.9.1045
235. Tsutsui H, Ishihara K, Cooper G (1993) Cytoskeletal role in the contractile dysfunction of hypertrophied myocardium. Science 260:682–687. https://doi.org/10.1126/science.8097594
236. Sato H, Nagai T, Kuppuswamy D et al (1997) Microtubule stabilization in pressure overload cardiac hypertrophy. J Cell Biol 139:963–973. https://doi.org/10.1083/jcb.139.4.963
237. Nishimura RA, Housmans PR, Hatle LK et al (1989) Assessment of diastolic function of the heart: background and current applications of doppler echocardiography. Part i. physiologic and pathophysiologic features. Mayo Clin Proc 64:71–81. https://doi.org/10.1016/s0025-6196(12)65305-1
238. Nishimura RA, Abel MD, Hatle LK et al (1989) Assessment of diastolic function of the heart: background and current applications of doppler echocardiography. Part ii. Clinical studies. Mayo Clin Proc 64:181–204. https://doi.org/10.1016/s0025-6196(12)65673-0

239. Kreitzer G, Liao G, Gundersen GG (1999) Detyrosination of tubulin regulates the interaction of intermediate filaments with microtubules in vivo via a kinesin-dependent mechanism. Mol Biol Cell 10:1105–1118. https://doi.org/10.1091/mbc.10.4.1105
240. Liao G, Gundersen GG (1998) Kinesin is a candidate for cross-bridging microtubules and intermediate filaments. J Biol Chem 273:9797–9803. https://doi.org/10.1074/jbc.273.16.9797
241. Cheng G, Takahashi M, Shunmugavel A et al (2010) Basis for MAP4 dephosphorylation-related microtubule network densification in pressure overload cardiac hypertrophy. J Biol Chem 285:38125–38140. https://doi.org/10.1074/jbc.m110.148650
242. Takahashi M, Shiraishi H, Ishibashi Y et al (2003) Phenotypic consequences of β 1 -tubulin expression and MAP4 decoration of microtubules in adult cardiocytes. Am J Physiology-Heart Circ Physiol 285:H2072–H2083. https://doi.org/10.1152/ajpheart.00396.2003
243. Guichard JL, Rogowski M, Agnetti G et al (2017) Desmin loss and mitochondrial damage precede left ventricular systolic failure in volume overload heart failure. Am J Physiology-Heart Circ Physiol 313:H32–H45. https://doi.org/10.1152/ajpheart.00027.2017
244. Lewis YE, Moskovitz A, Mutlak M et al (2018) Localization of transcripts, translation, and degradation for spatiotemporal sarcomere maintenance. J Mol Cell Cardiol 116:16–28. https://doi.org/10.1016/j.yjmcc.2018.01.012
245. Scarborough EA, Uchida K, Vogel M et al (2021) Microtubules orchestrate local translation to enable cardiac growth. Nat Commun 12:1547. https://doi.org/10.1038/s41467-021-21685-4
246. Scholz D, Baicu CF, Tuxworth WJ et al (2008) Microtubule-dependent distribution of mRNA in adult cardiocytes. Am J Physiology-Heart Circ Physiol 294:H1135–H1144. https://doi.org/10.1152/ajpheart.01275.2007
247. Goswami C, Hucho T (2008) Submembraneous microtubule cytoskeleton: biochemical and functional interplay of TRP channels with the cytoskeleton. FEBS J 275:4684–4699. https://doi.org/10.1111/j.1742-4658.2008.06617.x
248. Clemo HF, Stambler BS, Baumgarten CM (1999) Swelling-activated chloride current is persistently activated in ventricular myocytes from dogs with tachycardia-induced congestive heart failure. Circ Res 84:157–165. https://doi.org/10.1161/01.res.84.2.157
249. Kuroda J, Sadoshima J (2010) NADPH oxidase and cardiac failure. J Cardiovasc Transl 3: 314–320. https://doi.org/10.1007/s12265-010-9184-8