Mechano-Electric Coupling in the Heart: Effects on Heart Rate and Rhythm

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Abstract

Cardiac electrical and mechanical activity are closely interrelated, not only via the chain of events commonly referred to as 'excitation-contraction coupling' that links electrical excitation to contraction, but equally via feedback from the heart's mechanical environment to the origin and spread of cardiac excitation. The latter has been termed mechano-electric coupling and complements excitation-contraction coupling to form an intracardiac electro-mechanical regulatory loop. This chapter will explore the relevance of mechano-electric coupling in the heart by reviewing its pro- and anti-arrhythmic effects on heart rate and rhythm, and the underlying mechanisms that may account for clinical and experimental observations.

Keywords

Mechano-electric feedback · Sinoatrial node · Arrhythmia · Atrial dilation · Ventricular fibrillation · *Commotio cordis* · Precordial thump · Stretch-activated channel · Computational modelling

7.1 Introduction

The heart is a remarkably dynamic organ, whose efficient function depends on well-coordinated excitation and contraction, and their beat-by-beat adjustment to continuously fluctuating haemodynamic conditions. Incredibly, this auto-regulatory coordination and acute adaption to systemic requirements occur in the absence of neuro-muscular junctions (which are required for steering skeletal muscle activity) and continues to function after the removal of extracardiac neuro-hormonal inputs (for instance, when the heart is removed from the body).

This intracardiac autoregulation is driven by 'feedforward' and 'feedback' interactions between the heart's electrical and mechanical activity. In what is generally thought of as the

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forward direction, electrical excitation of the heart, which originates in the sinoatrial node (SAN) and spreads through the myocardium via intracellular coupling and specialised conducting pathways (atrioventricular node, bundles of His, Purkinje fibres), results in cellular contraction through a process known as 'excitation-contraction coupling (ECC)' [1, 2]. In the opposite direction, the heart's mechanical state, determined by internal and external parameters, affects cardiac electrical activity. This acute feedback is known as 'mechano-electric feedback' (when considering only the effects of the mechanical activity of the heart itself), or more broadly, 'mechano-electric coupling' (MEC, which includes responses to extracardiac mechanical inputs). MEC is thought to act through stretch-activated ion channels (SAC, which are directly gated by a mechanical stimulus) [3], as well as through stretch-modulated ion channels (whose normal activity is modulated by mechanical stimulation), changes in calcium (Ca^{2+}) handling, and mechano-sensitive second messenger systems (Fig. 7.1) [5, 6].

In this chapter, we will present the most striking clinical and experimental evidence for MEC and explore molecular mechanisms underlying these (patho-)physiological observations.

7.2 Mechanical Modulation of Heart Rate

7.2.1 Background

Modulation of heart rate (HR) by changes in venous return was reported over a century ago by Francis Bainbridge, who attributed HR acceleration upon venous fluid injection in anaesthetised dogs to a predominantly vagal autonomic reflex [7, 8]. His experiments established a correlation between HR response and central venous pressure (CVP) but not arterial pressure. Reconfirmation of this response in humans proved difficult, as most non-invasive interventions that change CVP also tend to affect arterial pressure. The latter may trigger dominant baroreceptor responses that stimulate contrasting HR effects (e.g., via the depressor reflex). Donald and Shepherd finally circumvented this problem and established the equivalent of a 'Bainbridge response' in humans, using passive leg-elevation of volunteers in the supine position to favour venous blood return to the trunk of the body. This raised CVP without measurably affecting arterial pressure, revealing a positive chronotropic effect on HR in human [9].

Since then, the Bainbridge response has also been observed in isolated hearts, right atrial preparations [10], sinoatrial node (SAN) tissue [11], and even single cardiac pacemaker cells [12]. Thus, local MEC mechanisms contribute to mechanical modulation of HR, beyond the originally-implied neural reflex response.

7.2.2 Clinical Observations

Human studies of the Bainbridge response have focussed on the assessment of respiratory sinus arrhythmia (RSA) in normal subjects and in heart transplant recipients.

RSA is a 'physiological arrhythmia', where HR is modulated during the respiratory cycle, increasing during inspiration (when low intrathoracic pressure aids not only air intake but also venous return) and decreasing during expiration (when output from the chest is favoured). RSA is reported to reduce pulmonary shunt effects and increase oxygen uptake, when compared to stable HR [13], indicating a possible role for mechanical HR modulation in normal physiology. RSA can be measured non-invasively by establishing respiratory rate-related frequency oscillations in the R-R intervals of the electrocardiogram. Two major peaks in HR frequency oscillations appear in healthy subjects at rest. A so-called high-frequency (HF) peak (0.15–0.3 Hz) is correlated with the respiratory cycle and is usually attributed to oscillations in 'vagal tone'. It is this peak which is considered to represent RSA. A second, low-frequency (LF) peak (~0.1 Hz), attributed to changes in 'sympathetic tone', is not modulated with each respiratory cycle.

As expected, transplant recipients (whose hearts no longer receive nervous system inputs) tend to lack the LF peak. A distinct HF peak is

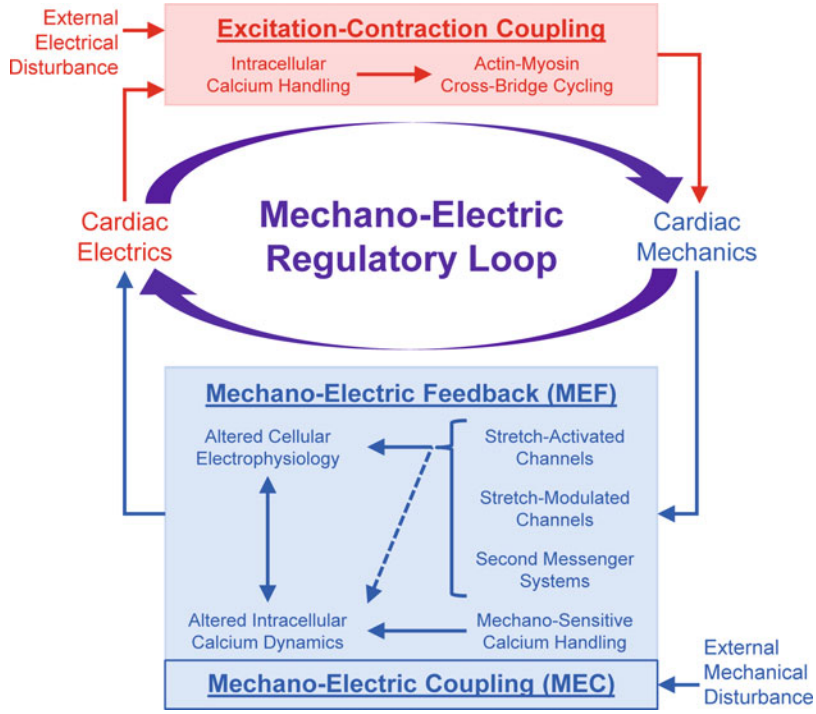

Fig. 7.1 The feedforward and feedback links between cardiac electrophysiology and mechanics forming an intracardiac mechano-electric regulatory loop. The feedforward between electrical excitation and mechanical contraction involving intracellular Ca^{2+} handling and actin-myosin cross-bridge cycling, is a process known as 'Excitation-Contraction Coupling' (top). Feedback (bottom) from myocardial deformation to cell electrophysiology and intracellular Ca^{2+} dynamics occurs via multiple interdependent mechano-sensitive mechanisms, which in turn affect the origin and spread of excitation, a phenomenon known as 'Mechano-Electric Feedback' (considering only cardiac mechanical activity as an input signal) or more broadly 'Mechano-Electric Coupling' (encompassing mechanical perturbations of the heart irrespective of their origin). (From [4], with permission)

still discernible, albeit at a reduced magnitude, suggesting that mechanisms intrinsic to the heart may contribute to RSA [14]. In support of this suggestion, tidal volume (and, therefore, venous return) modulates HR variability in these patients to a greater extent than changes in breathing rate.

Intrinsic HR modulation is not unique to transplant recipients. In normal subjects, the magnitude of both LF and HF oscillations is reduced during early exercise. As workload increases, the LF component diminishes and all but disappears at maximal workloads, whereas the HF peak increases in magnitude, despite the loss of 'vagal tone' associated with physical work [15]. This can be observed even after additional ganglion block [16], again suggesting intracardiac contributions to RSA. Interestingly, the delay between respiratory and HF oscillation peaks drops with exercise in normal subjects, rendering it similar to that in transplant recipients (in whom it remains unchanged), perhaps suggesting a switch from normally dominant longer-latency reflex loops to intrinsic cellular/tissue-level control [15].

Human studies, therefore, point towards the existence of an intracardiac mechano-sensitive HR control mechanism contributing to HR modulation through fluctuations in venous return. Elucidation of the stimulus for, and mechanisms of, this response requires experimental manipulation that would be impractical and/or unethical in humans.

7.2.3 Experimental Studies

The HR changes observed in humans have been reproduced in intact anaesthetised dogs, where SAN-specific stretch (applied via a weight and pulley system in open-chest experiments) can elicit instantaneous HR acceleration by >20%, which is not abolished by denervation or adrenergic and cholinergic block [17].

In the isolated rabbit heart, responses similar to those in intact preparations were described by Blinks, who observed that progressive increases in atrial pressure (up to ~100 mmHg) are accompanied by instantaneous HR acceleration in rabbit [10]. This response appears rapidly (within the first minute), plateaus by 2–3 min, and can be maintained for several hours. Interestingly, further atrial pressure increases beyond this (already supra-physiological) range result in HR deceleration.

Adrenergic or cholinergic block, sufficient to alter HR by 50% from baseline, have no effect on the HR response to changes in filling pressure in rat [18]. Neither do application of tetrodotoxin (a fast sodium [Na^+] channel blocker) or neonatal capsaicin injections (ablation of intracardiac neurons). This suggests that neither external autonomic nor intracardiac neuronal signalling is necessary for the intrinsic HR response to stretch. Finally, the high solution flow rates used in atrial preparations [10] and the speed of HR response suggest that humoral factors are unlikely to be key contributors.

In the 1960s, Deck observed beating rate (BR) changes during the distension of cat and rabbit isolated atrial tissue containing the SAN. Measuring the trans-membrane potential (V_m) of SAN pacemaker cells and the contractile behaviour of the tissue during uni-axial or equi-biaxial stretch [11], he observed a 15–20% BR acceleration upon stretch. This was accompanied by an instantaneous reduction in absolute amplitudes of both maximum systolic and maximum diastolic potentials (MSP and MDP, respectively), giving rise to a reduction in SAN action potential (AP) amplitude and in the duration of the spontaneous diastolic depolarisation phase. These direct electrophysiological observations of V_m changes in SAN tissue help to narrow down the range of plausible molecular mechanisms involved, as their effect would appear to be linked to an electrophysiological mechanism with a net reversal potential (E_{rev}) between the MDP and MSP of SAN pacemaker cells.

7.2.4 Underlying Mechanisms

Early single-cell studies into the mechanisms underlying mechanical modulation of HR used cell swelling as a mechanical stimulus. This was shown to activate a chloride current ($I_{Cl,swell}$), whose E_{rev} near 0 mV could conceivably confer the capacity to augment pacemaker frequency in response to mechanical stimulation [19]. However, $I_{Cl,swell}$ activates with a lag time of over 30 s in cardiac myocytes, rendering it too slow for acute beat-by-beat changes in HR. Furthermore, cell swelling is associated with an increase in cell diameter and negligible axial elongation (or even shortening). Micromechanically, this is fundamentally different from axial stretch, where lengthening at constant cell volume is associated with a reduction in cell diameter. In addition to these biophysical differences in stimulus, hypo-osmotic swelling of rabbit spontaneously beating SAN pacemaker cells actually reduces spontaneous BR [20]. Cell swelling is not an ideal approach, therefore, to probe acute mechanical modulation of cardiomyocyte electrophysiology in normal physiological conditions, where cardiomyocyte cell volume is not assumed to change. That said, acute cell swelling mimics certain aspects of cell behaviour in ischaemia and reperfusion which, together with pathologically remodelled cells (e.g., in hypertrophy, where $I_{Cl,swell}$ can be persistently activated in working myocardium [21]), may constitute meaningful research targets for this technique.

Axial stretch can be applied to single myocytes using a range of techniques to attach probes for mechanical stimulation. One approach is to use carbon fibres, which adhere to single cells without the need for gluing, tying, or suction [22]. Using

this technique, Cooper et al. observed a significant increase in BR of rabbit single SAN cells during 5–10% stretch. This was accompanied by a reduction in absolute values of MSP and MDP [12], reproducing previous SAN tissue results [11]. Voltage clamp studies revealed that stretch-activated a 6 nS/pF whole-cell current with an E_{rev} of –11 mV [12].

The properties of the stretch-activated current measured by Cooper et al. [12] are similar to the mechanically induced cation non-selective current (SAC_{NS}) reported in many other eukaryotic cells [3]. SAC_{NS} is carried by rapidly activating channels with E_{rev} approximately halfway between MDP and MSP [23]. SAC_{NS} opening will therefore depolarise diastolic, and re-polarise systolic V_m, potentially explaining the observed changes in SAN cell and tissue MSP and MDP during stretch.

A point of contention has been the observation that HR responses may differ between species. Most medium and large mammals (and other classes of animals, such as fish [24, 25]) respond to SAN stretch with HR acceleration, while smaller mammals have shown HR deceleration [26]. Interestingly, this discrepancy is not incompatible with a major contribution of SAC_{NS} to both responses. Larger animals (as well as fish) tend to have a more slowly beating SAN, with AP shapes that are characterised by a slow AP upstroke (carried by Ca^{2+} influx) and a prominent plateau-like phase, while smaller mammals with faster HR show a faster upstroke (with a significant contribution from fast Na^+ channels) and swift initial repolarisation, giving rise to a more triangular AP shape (Fig. 7.2). Thus, 'slow' SAN AP waveforms spend the majority of each cycle moving their V_m from MDP (or MSP) *towards* the E_{rev} of SAC_{NS}. Their faster counterparts spend a larger proportion of time moving their V_m*away* from E_{rev} of SAC_{NS}. Thus, one and the same mechanism—activation of SAC_{NS} by SAN stretch—may speed up slow HR *and* reduce already fast ones. This notion has been supported recently by experiments involving stretch of mouse-isolated SAN, in which lengthening of the AP plateau by block of rapidly activating potassium currents with 4-aminopyridine shifted the stretch-induced change in BR from slowing to acceleration [28].

Ideally, the insight obtained by the reduction of a problem from whole animal to tissue, cells and channels is complemented by re-integration, from putative mechanisms to systemic response [29]. This can be achieved using conceptual consideration, or better, quantitative mathematical models [30] and experimental investigation (e.g., via application of selective pharmacological probes). Computational modelling of stretch effects on SAN cell activity has confirmed the *plausibility* of SAC_{NS} contributions as a key to stretch-induced BR changes [12]. Experimental proof calls for selective inhibition (or activation) of SAC_{NS}. At present, available pharmacological tools are limited. Gadolinium ions are potent SAC_{NS} blockers, but they also affect other ion channels and precipitate in physiological buffers. At low concentrations (<50 μM), streptomycin is both potent and reasonably selective when used on isolated cells, but its utility for acute SAC_{NS} block in multicellular preparations has been called into question (if streptomycin did act as an acute SAC_{NS} blocker in situ, we could probably not prescribe it to patients) [26]. The most specific SAC_{NS} blocker, *Grammostola spatulata* mechanotoxin-4 (GsMTx-4), is a peptide isolated from a tarantula toxin [31]. It has been found to reversibly block stretch-induced BR changes in guinea pig and mouse SAN tissue, without affecting background force [26]. One should remember, however, that quantitative plausibility is no substitute for experimental validation [32], and mechano-sensitivity of other currents involved in pacemaking, or changes in intracellular signalling, may also contribute to SAN stretch responses [33–36].

The magnitude of mechanical effects on HR appears to increase with the structural complexity of the biological model (isolated SAN cells ~5%, whole-heart/SAN tissue ~15%, intact dog up to 30% [26]). Probable explanations include: (1) the increasing loss of structures involved in the transmission of mechanical stimuli to molecular effectors as one reduces the biological model system [28]; (2) increasing deprivation of possible paracrine effects, such as may be mediated by

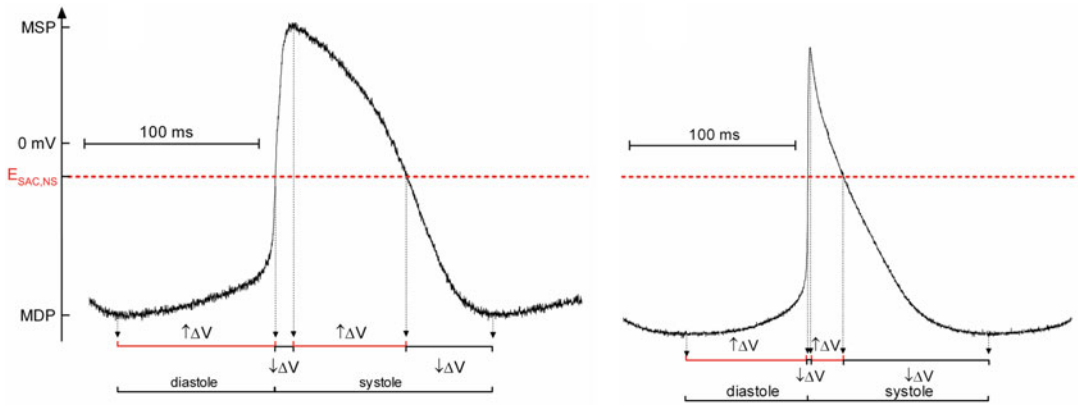

Fig. 7.2 Species differences in the theoretical effects of SAC_{NS} on the SAN cell AP. Membrane potential recordings illustrate the interrelation of cell electrophysiological parameters (MSP and MDP) and the SAC_{NS} reversal potential ($E_{SAC,NS}$). Time periods during which SAC_{NS} activation would either accelerate (↑ΔV) or slow (↓ΔV) intrinsic changes in SAN cell membrane potential are labelled. Left: rabbit SAN cell; right: mouse SAN cell. The rabbit SAN cell spends ~71% of cycle duration in ↑ΔV, whereas in the mouse, this phase accounts for just ~46%. (From [27], with permission)

endothelial cells, which are prone to suffer from tissue isolation and are removed by cell separation; or (3) removal of inter-cellular electrotonic coupling between identical and/or different cell populations. For instance, human fibroblasts have been found to contain SAC_{NS} [37], and functional electrotonic coupling has been shown to exist between fibroblasts and myocytes in native cardiac tissue [38, 39], including the SAN [40]. The possibility that fibroblasts may be important for stretch-induced changes in HR is supported by computational modelling, which predicts that stretch-modulation of fibroblast V_m could accelerate diastolic depolarisation in electrotonically coupled SAN myocytes by >20% [41]. Similar considerations may apply for macrophages, which have also been shown to be mechano-sensitive [42] and can electrotonically couple to cardiomyocytes, affecting their electrical activity [43, 44].

Finally, intrinsic cellular MEC responses could be amplified in vivo by interaction with autonomic signalling. Atrial pressure increases of just 2 mmHg, for example, induce both HR acceleration and a significant reduction in the percentage response to vagal stimulation in intact rabbit [45], effectively reducing the influence of underlying vagal tone. Thus, local and systemic HR modulation occur in conjunction and may amplify, or dampen, each other's effect.

7.2.5 Summary

The intrinsic HR response to stretch, such as caused by changes in venous return, is demonstrable at physiologically-relevant levels of mechanical stimulation, over multiple spatial scales. Intrinsic control has been estimated to contribute >30% of RSA during exercise in healthy individuals [16]. The evolutionary advantage of such a mechanism has been speculated to arise from earlier beat induction in response to cardiac filling (haemodynamic benefit), from improving cardiac pump function (which is more mechanically efficient when working at smaller radii), and/or from maximising pulmonary gas exchange (with reduced shunt volume) [13]. Alternatively, stretch effects on HR could be a side-effect of mechanisms that underlie mechanical modulation of contractile force [46].

Future investigations should consider the mounting evidence suggesting that SAN pacemaker rate depends not only on trans-sarcolemmal ion fluxes but involves an intracellular Ca^{2+} redistribution, driven by the release of

Ca^{2+} from the sarcoplasmic reticulum, followed by trans-sarcolemmal inward currents such as via the Na^+/Ca^{2+} exchanger [47]. Of note, stretch has been shown to increase sarcoplasmic reticulum Ca^{2+} release in ventricular cells [48–50], which—if present in SAN—could be relevant for the mechanical modulation of heart rate.

7.3 Pro-arrhythmic Effects of Mechanical Stimulation

7.3.1 Background

First observations that perturbation of the heart's mechanical status may initiate deadly cardiac arrhythmias were published nearly 150 years ago, with reports of sudden cardiac death associated with non-penetrating impact to the precordium (*Commotio cordis*, CC; for review, see [51]). More recently, rhythm disturbances due to internal mechanical stimulation during cardiac catheterisation have been observed [52]. It is now also believed that cardiac tachyarrhythmias, encountered in pathologies associated with non-uniform contraction, tissue remodelling, and/or volume or pressure overload are, in part, caused by electrophysiological responses to the altered mechanical environment [4, 5]. Arrhythmogenic effects of stretch on cardiac electrophysiology have been investigated in isolated whole heart, tissue and cellular models, helping to elucidate underlying mechanisms [5, 53].

7.3.2 Clinical Observations

Reports about pro-arrhythmic effects of acute external mechanical stimulation by CC [51], occasionally occurring during chest compressions soon after electrical defibrillation [54], together with cases of ectopy induction upon intracardiac catheter contact [52], suggest that heart rhythm disturbances can be related to intracardiac MEC effects. In vivo evidence also indicates that arrhythmogenic mechanical stimulation can be local or global. For instance, an increase in ventricular load by transient aortic occlusion during cardiac surgery has been shown to reduce longitudinal shortening and increase mechanical dispersion, which is associated with AP shortening and a pro-arrhythmic increase in local dispersion of AP duration [55], while balloon inflation during pulmonary valvuloplasty is associated with the induction of ventricular ectopy [56]. The same is true for the atria, where acute changes in volume loading have been found to increase the incidence and sustenance of arrhythmias [57]. Changes in atrial electrophysiology have also been seen with acute drops in atrial pressure during balloon commissurotomy for mitral stenosis and atrial flutter, as well as with short-term dual chamber pacing [57].

Effects of chronic stretch are usually observed in patients with sustained ventricular pressure or volume overload. Hypertension, congestive heart failure, and dilated cardiomyopathy are all associated with a high incidence of arrhythmias [58, 59]. It is difficult to assess, in these cases, whether mechanical stimulation directly contributes to rhythm disturbances or whether it acts via structural and functional tissue remodelling [60]. However, the observations that average daily blood pressure is highly correlated with the risk of ventricular tachyarrhythmias in heart failure patients [61], and that acute temporary removal of ventricular overload (e.g., by the Valsalva manoeuvre) can terminate chronic ventricular tachycardia [62], suggest that mechanical factors may play a role in the chronic setting.

7.3.3 Experimental Studies

Depolarisation of V_m by acute diastolic stretch has been demonstrated in isolated hearts, as well as in ventricular and atrial tissue and cell preparations [5]. In isolated hearts, a transient increase of intraventricular volume during diastole results in membrane depolarisation, which, if sufficiently large and rapid, can trigger premature ventricular excitation [63] and short periods of ventricular tachycardia (VT) [64].

The effects of acute systolic stretch are more complex. Both shortening and prolongation of the AP have been observed, along with early after-

depolarisation-like events, both in isolated cardiomyocytes and multicellular experimental preparations [5]. In the setting of CC, non-penetrating precordial impacts can induce rhythm disturbances in the absence of structural damage to the heart. The severity of arrhythmias, including ventricular fibrillation (VF), changes in an impact magnitude- and timing-dependent manner. This was first investigated experimentally some 90 years ago by Schlomka et al., who found that impacts to the precordial region of anaesthetised rabbits, cats, and dogs result in ectopic excitation and, in 20% of cases, VF [65, 66]. Importantly, they showed that mechanical induction of arrhythmias is not affected by bilateral vagotomy, indicating that arrhythmogenesis is not a result of a parasympathetic reflex. Furthermore, arrhythmia induction depends on the region of impact (mid and lower sternum are the most susceptible areas, especially for VF), the size of the contact area (smaller impact areas result in more severe rhythm disturbances), and the duration of the impact (rapid impacts are most arrhythmogenic). More recently, in a swine model of CC, Link et al. confirmed the importance of impact site, size, and severity and showed that only impacts during the early T-wave result in VF, while impacts at other times of the cardiac cycle produce various other transient rhythm disturbances [67]. A similar response has been demonstrated with a rapid increase in intraventricular volume in isolated rabbit hearts [68]. Acute volume loading has been shown to decrease conduction velocity, both in ventricles [69] and atria [57], which can contribute to the initiation and maintenance of arrhythmias. With volume loading of the atria, a reduction in AP duration and refractoriness, and an increase in dispersion of refractoriness, have been demonstrated, increasing the vulnerability to atrial fibrillation [57]. This can be prevented by acute atrial unloading [70]. Interestingly, it has been shown (by one of the editors of this book under her maiden name Theophile) that stretch of Purkinje fibres speeds up their rate of spontaneous diastolic depolarisation [71], while increasing conduction velocity [72], potentially leading to stretch-induced ectopy [71]. Other cardiac cell types, such as fibroblasts [41], pulmonary vein muscle cells [73], valve cells [74], chondrocytes, smooth muscle and endothelial cells [75], macrophages [42], and intracardiac neurons [76] are also mechano-sensitive, suggesting that the interplay between different cell types in the heart may be relevant for stretch-induced arrhythmogenesis, an important concept that has been insufficiently explored.

The similarity of effects of precordial impact and rapid intraventricular pressure increase raises an interesting question about the relative contribution of local versus global stretch to electrophysiological responses. This is highlighted by the large change in intraventricular pressure (brief spikes of more than 500 mmHg seen with precordial impact in the swine model), whose magnitude has been correlated with the probability of VF induction in vivo (maximum effects between 250 and 450 mmHg) [77]. Myocardial compliance varies throughout the ventricle (which may also be affected by regional differences in coronary vascular pressure), so gross changes in intraventricular pressure or volume will result in a heterogeneous distribution of tissue stretch. This is supported by the observation that intraventricular volume changes yield non-uniform depolarisation, with the origin of any stretch-induced excitation most often in the posterolateral region of the left ventricle, typically an area of high compliance [63]. The only published data of intraventricular activation sequence during extracorporeal CC impacts from a single pig experiment suggests focal excitation of the ventricle right underneath the impact site. This suggests a more directly impact site-related mechanism and reemphasises the question of the relative causal contributions of global and local stretch to arrhythmogenesis [78].

In isolated heart models, large intraventricular pressure pulses (between 200 and 280 mmHg) have been used to trigger VF [68]. At the same time, local low-energy non-traumatic impacts, timed with the early T-wave, can induce VF in isolated guinea pig [79] and rabbit hearts [80]. Epicardial optical mapping revealed the presence of deformation-magnitude-dependent focal activation [80, 81]. This results in VF only

when there is spatiotemporal overlap of the mechanical stimulus with the trailing wave of repolarisation [80], as predicted in prior modelling work (see next section) [82].

The idea that the structural heterogeneity of ventricular tissue modulates globally applied stretch to create heterogeneous strain distributions and focal sites of excitation that lead to initiation of re-entrant arrhythmias is further supported by a study that used optical mapping with stretch applied across a right ventricular tissue flap [83]. This demonstrated that focal excitation originates at the point of largest strain differences, which can result in sustained re-entrant tachyarrhythmias. Similarly, an increase in the probability of mechanically induced excitation in areas showing paradoxical segment lengthening has been observed in diseases with heterogeneous changes in ventricular compliance, such as regional ischaemia [84] and infarction [85]. In acute regional ischaemia, the degree of dilation of the acutely ischaemic tissue is a strong predictor of the probability of arrhythmogenesis, including VF [86]. The role of heterogeneous stretch in VF induction is further supported by experiments showing that acute localised stretch increases the complexity of VF activation maps, with more areas of conduction block and breakthrough patterns [87]. Such heterogeneities in stress-strain distribution would result in significant differences in mechanical stimulation of cells, which could give rise to local ectopic foci and regions of functional block.

7.3.4 Underlying Mechanisms

Pro-arrhythmic effects of myocardial stretch can be explained, in part at least, by SAC activation. Two sub-categories of SAC can be distinguished in myocardium: SAC_{NS}, which allow passage of various cations (E_{rev} usually between 0 and –20 mV), and potassium-selective SAC_K (E_{rev} near –90 mV; for review see [88]). During diastolic stretch, V_m tends to show depolarisation (Fig. 7.3), which can be explained by a predominant contribution of SAC_{NS} (SAC_K would cause diastolic hyperpolarisation, which is not seen in cardiac cells). Systolic stretch primarily accelerates AP repolarisation, which could be caused by either SAC sub-type [90].

A predominant contribution to stretch-induced changes in V_m by SAC_{NS} is further supported by the observation that MEC effects can be eliminated in ventricles [80, 91] and atria [57] by pharmacological block of this channel. In turn, activation of SAC_{NS} is sufficient to trigger AP generation in isolated cardiomyocytes [92]. Interestingly, SAC_{NS} blockers do not prevent the reduction in refractory period seen with atrial pressure-loading of the isolated heart, suggesting that SAC_K may contribute to responses in that setting [93].

Relative contributions of SAC_{NS} and SAC_K to impact-induced VF have remained controversial. The vulnerable window for VF induction coincides with a period of pronounced heterogeneity in ventricular V_m and refractoriness. Mechanical stimulation, in this setting, depolarises cells that have regained excitability (presumably a SAC_{NS} effect, potentially giving rise to ectopic foci), while in other cells that are still more depolarised the time-course of repolarisation is altered (possibly through both SAC_{NS} and/or SAC_K effects, increasing heterogeneity in refractoriness). The former may provide the trigger, and the latter a sustaining mechanism for arrhythmias, including VF. Among experimentally proposed contributors is the ATP-dependent potassium channel (K_{ATP}), whose open probability is also modulated by stretch [94]. In the presence of glibenclamide (to block K_{ATP}), the incidence of VF upon precordial impact is significantly reduced in pig. At the same time, impacts during the T-wave still trigger premature ventricular contractions, highlighting the continued ability to mechanically induce an arrhythmogenic trigger [95]. Application of streptomycin in the same animal model did not affect VF inducibility [96], but as mentioned before there is potential for false-negative interpretation of data obtained with systemic streptomycin application (as it doesn't block SAC_{NS} well in intact tissue). In rabbit isolated hearts, block of SAC_{NS} with GsMTx-4 was indeed effective in preventing mechanically induced VF [80]. Thus, activation of SAC_{NS} seems to be a necessary contributor to CC.

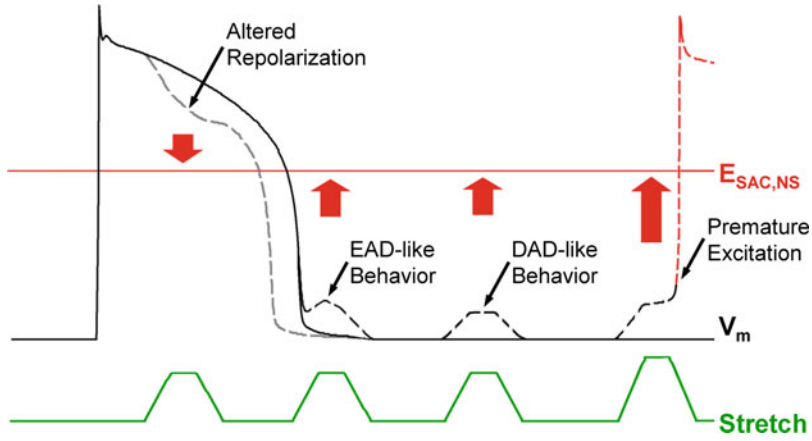

Fig. 7.3 Schematic representation of transient stretch effects on whole-cell V_m. SAC_{NS} have a reversal potential ($E_{SAC,NS}$) about halfway between plateau and resting potentials. Depending on the timing of mechanical stimuli (bottom curve), SAC_{NS} activation may shorten AP duration, cause early or delayed after-depolarisation-like behaviour, or—if strong enough—trigger excitation (top curve). The reversal potential of SAC_K is negative to resting V_m. Their activation, during *any* part of the cardiac cycle, would tend to re- or hyperpolarise cardiac cells, in particular during the AP plateau (when their electrotonic driving force is largest). Given that diastolic stretch, if it causes any change in V_m at all, tends to depolarise resting cells, thus this response appears to be dominated by SAC_{NS} under normal circumstances. (From [89], with permission)

The principal electrophysiological consequences of cardiac MEC have been reproduced in various computational models of cardiomyocyte SAC effects [97]. These formulations have been integrated into two- [82] and three-dimensional models [98] of ventricular tissue, which suggest that sustained re-entry is observed only if a mechanical stimulus (1) encounters tissue that has regained excitability (so that a mechanically-induced ectopic focus can arise), (2) overlaps with the trailing wave of repolarisation (so that local AP prolongation gives rise to an area of the functional block at the intersection of the preceding and new excitation wave), and (3) extends into tissue that is still at more positive V_m levels (so that regional AP shortening may help to sustain the arrhythmia). This would explain why the most severe expression of CC, sudden cardiac death from VF, is rare in real life. The view that ischaemic segment lengthening may be responsible for mechanically induced excitation and re-entry has also been supported by three-dimensional computational modelling, suggesting that premature ventricular excitation originates from the ischaemic border because of mechanically induced depolarisation [99]. These computational predictions form interesting targets for further experimental assessment.

7.3.5 Summary

Stretch of the myocardium, whether acute or chronic, has pronounced effects on cardiac electrophysiology. This can contribute to induction and sustenance of cardiac arrhythmias. Experimental models have reproduced the effects of stretch on heart rhythm in single cells, tissue preparations, isolated hearts and whole animals, demonstrating that a significant proportion of mechanically induced changes in heart rate and rhythm can be explained by intracardiac MEC. Experimental and computational work strongly suggests a role for SAC in these responses. In addition to mechanically *gated* SAC, most ion channels in the heart can be *modulated* by the mechanical environment [100], which complicates the picture, in particular as longer-term responses mediated via altered intracellular

ion concentrations are concerned. In addition, effects of heterogeneous stretch on myocardial Ca^{2+} handling have been shown to independently act as sources of ectopic excitation (for a review, see [101]). The molecular mechanisms by which ion channels (and Ca^{2+} handling proteins) sense mechanical changes, as well as their individual roles in the generation of arrhythmias, may, in the long run, help to devise new pharmacological and device therapies to treat diseases associated with stretch-induced changes in cardiac electrophysiology.

7.4 Anti-arrhythmic Effects of Mechanical Stimulation

7.4.1 Background

Schott's observation that a forceful blow to the chest wall (precordial thump, PT) could restore a palpable pulse of a patient in ventricular standstill during a Stokes-Adams attack, published in 1920, is believed to have been the first report on anti-arrhythmic effects of mechanical stimulation in the Western medical literature [102]. Since then, mechanical resuscitation has been attempted using a range of interventions. However, even though PT has been a documented part of European clinical practice for much of the past century, there is little agreement on the mechanisms and clinical utility of mechanical cardioversion.

7.4.2 Clinical Observations

Anti-arrhythmic mechanical stimulation has been observed in various clinical settings [103]. In his studies of 'intracardiac therapy' in the 1930s, Hyman found that the mechanical interaction of a needle with the myocardium could induce contractile activity [104]. Similarly, direct myocardial contact with catheters can cause ectopic excitation, with case reports illustrating termination of VT, ventricular bradycardia [52], and even atrial fibrillation [105]. Cardiac mechano-sensitivity is also exploited by cardiac surgeons when weaning the heart from cardiopulmonary bypass, where finger tapping of the heart may serve to restore rhythmic contractile activity, in particular after failed electrical defibrillation. Extracorporeal mechanical stimuli can trigger contractions in ventricular standstill [106], for example, to maintain consciousness in cardiac arrest victims [107] and (although less reliably) terminate VT and VF [108]. Several reports have also found a link between an abrupt increase in intra-thoracic pressure (due to coughing [109] or the Valsalva manoeuvre [62]) and termination of tachyarrhythmias, although contributions by the nervous system and/or improved coronary perfusion have not been differentially assessed.

7.4.3 Experimental Studies

The use of cardiac catheterisation to terminate sustained cardiac arrhythmias was systematically explored in patients by Befeler [52], who showed that catheter tip stimulation of atrial and ventricular muscle is effective in reverting various rhythm disturbances (24% of atrial tachycardia cases, 60% of junctional tachycardias, and 14% of VT).

The success rate of PT has been studied with highly variable results. In the report by Befeler, 27% of VT cases were successfully treated with PT [52], while other investigations have shown success rates exceeding 40% [110]. Only a handful of prospective studies on PT effects have been published, all of which demonstrated vanishingly low success rates of tachyarrhythmia termination by PT (below 2%) [111–114]. However, the use of PT may be more promising in the asystolic heart, where PT-induced restoration of spontaneous circulation was found in 50% of asystolic cardiac arrest victims (although this study suffers from low n-numbers, so extrapolation to practice should be done with care) [114].

The (limited) clinical utility of PT in the setting of VF [115] appears to be related to time-since-collapse, as all reported successful cases of PT-induced cardioversion occurred very early during the development of VF, either at the verge of VT deterioration [116] or within the first few seconds of VF [52]. Animal models of PT

have shown a similar disparity of results, with success rates ranging from 0% in an asphyxiated dog model [117] to 95% in a post-infarction pig model [118], suggesting that the utility of PT may be inversely related to myocardial tissue energy supply. Also, in keeping with clinical data, repetitive extracorporeal mechanical stimuli in a pig model of cardiac standstill have been shown to be an effective means to mechanically pace the heart [119].

7.4.4 Underlying Mechanisms

The mechanisms underlying mechanical induction of ectopic excitation in the asystolic heart have been discussed above, and similar mechanisms may underlie PT pacing of patients in ventricular standstill. The dynamic interaction of SAC effects with ectopic foci and/or re-entrant excitation in the tachycardiac heart is more complex.

During mechanical stimulation in VT and VF, cells in the excitable gap(s) will be near the resting V_m, while others will be at various stages of the AP (somewhat like in the setting of CC, only that there will be multiple waves that co-exist in the tissue). Stretch of resting cells, if of sufficient amplitude, may cause excitation and obliterate the excitable gap. In cases where no re-entrant circles survive and no new ones are created by the intervention, this may terminate the arrhythmia. Computational simulations have shown that this conceptual view is biophysically plausible, using two- [97] and three-dimensional models [120]. Interestingly, these simulations also highlight how reduced availability in energy substrates may render PT less efficient. This is mediated via an ATP-reduction induced 'pre-conditioning' of K_{ATP} channels, which activate more readily upon mechanical stimulation in ischaemic conditions [121]. In the models, mechanical co-activation of K_{ATP} channels shifts the whole-cell 'net' E_{rev} towards more negative potentials, compared to what would be encountered with SAC_{NS} activation alone. This shortens AP duration and reduces the ability of mechanical stimulation to obliterate excitable gaps by depolarisation, with eventual failure to terminate re-entry, as observed in the setting of severe hypoxia [117].

7.4.5 Summary

The anti-arrhythmic effects of mechanical stimulation in various settings have been known to medical practitioners for over a century. PT can be utilised to pace the asystolic heart or, less successfully, to terminate tachyarrhythmias. These beneficial effects have been attributed to SAC_{NS} activation. However, reported success rates vary drastically, and even though PT can be quickly and easily applied, recent international resuscitation guidelines have de-emphasised PT as an emergency intervention in cardiac arrest [122, 123]. There is a concern, also, regarding the timing of PT, due to potential pro-arrhythmic effects of mechanical stimulation. The idea, however, that ill-timed PT would easily convert VT to VF has not been confirmed in most studies, except in the setting of pre-existing severe hypoxia [117]. Overall, reported PT side effects have been rare and minor. The variable success rates of PT may be related to a lack of training and/or variability in energy delivery by individuals applying PT. The scarcity of prospective study data calls for further research, to help identify the clinical utility of PT, and to explore the potential for more sophisticated mechanical interventions in emergency medicine and anti-arrhythmic therapy.

7.5 Conclusion

The heart is an integrated electro-mechanical system. Firmly established mechanisms underlying cardiac MEC effects include mechanical modulation of trans-sarcolemmal ion fluxes and intracellular Ca^{2+}handling. MEC affects heart rate and rhythm, from venous return-mediated changes in SAN pacemaker rate, to stretch-induced induction or termination of arrhythmias.

What is less clear is the physiological relevance of MEC [124]. Of course, from a regulation

theory point of view, ECC *should* be complemented by an intracardiac feedback pathway from mechanics to electrics [125]. But perhaps many of the 'most striking' examples of MEC effects on electrophysiology are, in fact, secondary to mechanisms involved in the mechanical modulation of contractility. Strategies successfully employed in skeletal muscle force grading, such as spatial recruitment or temporal summation of muscle fibre contractility, are ill-suited for the heart, where all cells contract during every cardiac cycle, where long AP plateaus cover most or all of the period during which cytosolic free Ca^{2+} is elevated, and where neuro-muscular junctions for individual cells are missing. Thus, cardiac myocytes must be able to actively adjust their own contractility to locally prevailing, and dynamically changing, mechanical demands. If this involved mechanisms (such as SAC) that—in response to distension (or reduced active cell shortening)—allowed a cardiomyocyte to preserve or gain Ca^{2+} (whether directly or indirectly via Na^+ influx with knock-on effects on Na^+/Ca^{2+} exchanger flux balance), then that would offer an evolutionary advantage. This advantage for autoregulation of *mechanics* may well be more important than the associated 'side-effect' on *electrics* of inward currents, which carry a risk of triggering ectopic excitation or of contributing to the sustenance of tachyarrhythmias.

Clearly, cardiac bi-directional electro-mechanical cross-talk is an area for further study. What is without question is that the heart is an exquisitely mechano-sensitive organ, and that this mechano-sensitivity has direct effects on heart rate and rhythm.

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