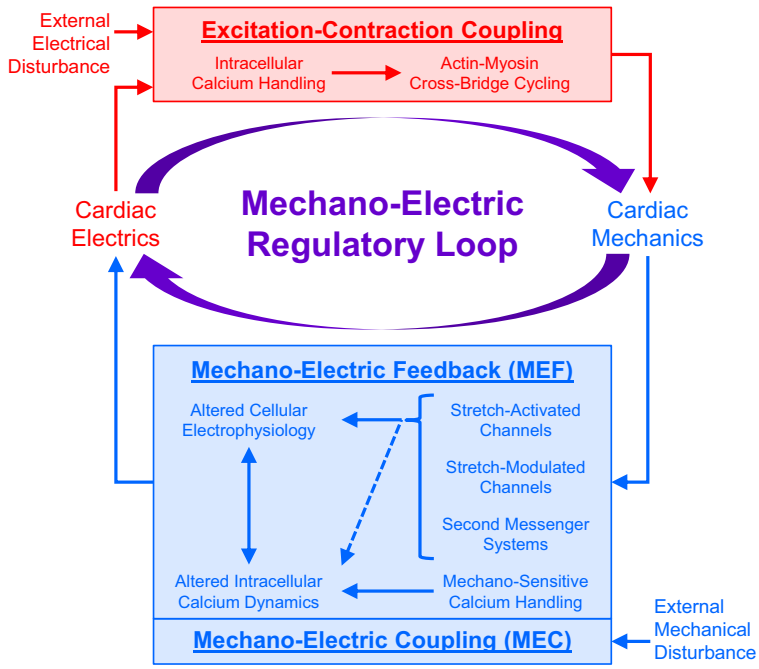
Physiological Reviews Review Article

CARDIAC MECHANO-ELECTRIC COUPLING: ACUTE EFFECTS OF MECHANICAL STIMULATION ON HEART RATE AND RHYTHM

GRAPHICAL ABSTRACT



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KEYWORDS

arrhythmias; autoregulation; cardiac; mechano-electric coupling; stretch

CLINICAL HIGHLIGHTS

1. Cardiac rhythm requires coordination of billions of heart cells' activity and swift adaption to changes in physiological demand. A critical factor involved is an intra-cardiac, electro-mechanical auto-regulatory loop, involving feedforward and feedback between electrical and mechanical behavior, including acute influences of the mechanical environment on electrophysiology (mechano-electric coupling).
2. In pacemaker cells, acute stretch (e.g., increase in venous return) results in more rapid diastolic depolarization, increasing heart rate (Bainbridge effect). This response is intrinsic to pacemaker cells and is critical for beat-to-beat adaptation. Age- and disease-related changes in myocardial mechanics can affect this response, contributing to sinoatrial node dysfunction and cardiac rhythm disturbances.
3. In the atria, acute stretch (e.g., volume/pressure overload) increases vulnerability to, and sustainability of, atrial fibrillation. This effect has been attributed to inhomogeneous, mechanically induced changes in cellular and tissue electrophysiology, caused by the highly heterogeneous issue architecture.
4. In the ventricles, acute mechanical stimulation can lead to tachyarrhythmias. Outcomes depend on the interrelation between stimulus and underlying electrophysiology, creating spatio-temporally defined vulnerable windows. In chronic diseases, stretch contributes to arrhythmias, as evidenced by the anti-arrhythmic effect of temporary ventricular unloading.
5. Transcutaneous mechanically induced excitation is an effective means for transient pacing of the asystolic/bradycardic heart, but not for tachyarrhythmia termination. Current guidelines indicate that fist pacing may be considered in hemodynamically unstable bradyarrhythmias and that there is insufficient evidence to recommend the use of precordial thump for witnessed asystole, making this an area requiring targeted research.

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CARDIAC MECHANO-ELECTRIC COUPLING: ACUTE EFFECTS OF MECHANICAL STIMULATION ON HEART RATE AND RHYTHM

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Department of Physiology and Biophysics and School of Biomedical Engineering, Dalhousie University, Halifax, Nova Scotia, Canada; Institute for Experimental Cardiovascular Medicine, University Heart Centre Freiburg/Bad Krozingen, Medical Faculty of the University of Freiburg, Freiburg, Germany; and CIBSS–Centre for Integrative Biological Signalling Studies, University of Freiburg, Freiburg, Germany

Quinn TA, Kohl P. Cardiac Mechano-Electric Coupling: Acute Effects of Mechanical Stimulation on Heart Rate and Rhythm. *Physiol Rev* 101: 37–92, 2021. First published May 7, 2020; doi: 10.1152/physrev.00036.2019.—The heart is vital for biological function in almost all chordates, including humans. It beats continually throughout our life, supplying the body with oxygen and nutrients while removing waste products. If it stops, so does life. The heartbeat involves precise coordination of the activity of billions of individual cells, as well as their swift and well-coordinated adaption to changes in physiological demand. Much of the vital control of cardiac function occurs at the level of individual cardiac muscle cells, including acute beat-by-beat feedback from the local mechanical environment to electrical activity (as opposed to longer term changes in gene expression and functional or structural remodeling). This process is known as mechano-electric coupling (MEC). In the current review, we present evidence for, and implications of, MEC in health and disease in human; summarize our understanding of MEC effects gained from whole animal, organ, tissue, and cell studies; identify potential molecular mediators of MEC responses; and demonstrate the power of computational modeling in developing a more comprehensive understanding of "what makes the heart tick."

arrhythmias; autoregulation; cardiac; mechano-electric coupling; stretch

1. Cardiac rhythm requires coordination of billions of heart cells' activity and swift adaption to changes in physiological demand. A critical factor involved is an intra-cardiac, electro-mechanical auto-regulatory loop, involving feedforward and feedback between electrical and mechanical behavior, including acute influences of the mechanical environment on electrophysiology (mechano-electric coupling).
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3. In the atria, acute stretch (e.g., volume/pressure overload) increases vulnerability to, and sustainability of, atrial fibrillation. This effect has been attributed to inhomogeneous, mechanically induced changes in cellular and tissue electrophysiology, caused by the highly heterogeneous issue architecture.
4. In the ventricles, acute mechanical stimulation can lead to tachyarrhythmias. Outcomes depend on the interrelation between stimulus and underlying electrophysiology, creating spatio-temporally defined vulnerable windows. In chronic diseases, stretch contributes to arrhythmias, as evidenced by the anti-arrhythmic effect of temporary ventricular unloading.
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I. CARDIAC MECHANO-ELECTRIC COUPLING

A. Mechano-Electric Coupling and the Mechano-Electric Regulatory Loop

The heart is a remarkably dynamic, robust organ. It beats approximately once per second and ~3–4 billion times in one's lifetime. In doing so, it pumps the equivalent to the volume contained in an Olympic-sized swimming pool each year. The human heart is composed of billions of individual muscle cells (cardiomyocytes), as well as a host of other cell types (e.g., fibroblasts, endothelial, fat, nerve, and immune cells). For effective pumping, this myriad of cells functions in a tightly controlled and well-orchestrated manner. Cardiomyocytes are electrically excited and mechanically contract in a well-coordinated pattern, while simultaneously adjusting their activity on a beat-by-beat basis to fluctuating

hemodynamic conditions so that local mechanical activity matches global circulatory demand. This demand is altered by exercise, when we change posture, and even with every breath we take, affecting the passive mechanical stretch of cells before contraction (referred to as "strain" when normalized to resting length) and the load against which cells actively contract (referred to as "stress" when expressed as force per cross-sectional area). In the ventricles, precontraction stretch can be approximated by end-diastolic volume (called "preload"), and the force opposing ventricular ejection is determined by the pressure in the downstream aortic or pulmonary vessels (called "afterload"). One result of the inherent cardiac mechano-sensitivity is the fact that cardiac output (ejection) matches venous return (filling), maintaining balanced cardiovascular system performance, while also matching the throughput of left and right sides of the heart over any period of time.

Incredibly, the heart's coordinated activity and its adaption to hemodynamic changes occur in the absence of the kind of neuromuscular junctions that organize skeletal muscle activity (although neuromuscular interaction sites with the autonomic nervous system may be much more widespread and regular in the heart than previously thought (478)). And while heart function is clearly influenced by extracardiac factors such as sympathetic and parasympathetic innervation and circulating hormones, beat-by-beat adaptation of cardiac function to changes in the mechanical environment continues even when the heart is removed from the body, or when it lacks nervous system inputs such as in freshly transplanted hearts. This is possible because the heart possesses highly efficient intrinsic (intracardiac) autoregulatory mechanisms that are based on feedforward and feedback interactions between the heart's electrical and mechanical activity.

In the direction classically regarded as feedforward, electrical excitation of the myocardium, physiologically initiated by the leading pacemaker in the sinoatrial node (SAN, a region of the right atrium), results in a spreading wave of cellular action potentials (AP) that, through a process known as excitation-contraction coupling, give rise to mechanical activation (47, 168). In the opposite direction, the heart's mechanical status, including internal and external mechanical perturbations, affects cardiac electrical activity. This acute feedback [as opposed to medium-term gene expression changes or longer term electrophysiological, mechanical, and structural remodeling that occur with chronic mechanical alterations and during heart disease (397)] has been termed "mechano-electric feedback" (which, strictly, considers only cardiac mechanical activity as an input signal), or more broadly, "mechano-electric coupling" (MEC, which encompasses mechanical perturbations of the heart irrespective of their origin) (318, 499) (illustrated in **FIGURE 1**).

MEC is an expression of the heart's exquisite mechano-sensitivity. It is evident at all levels of structural and functional integration (from subcellular to whole organ), in numerous cell types (ventricular and atrial myocytes, SAN and Purkinje pacemaker cells, as well as cardiac non-myocytes), and it is present both in invertebrates and vertebrates from fish to humans (318). Mechanical stimuli, acting through stretch-activated ion channels (SAC, which are directly gated by a me-

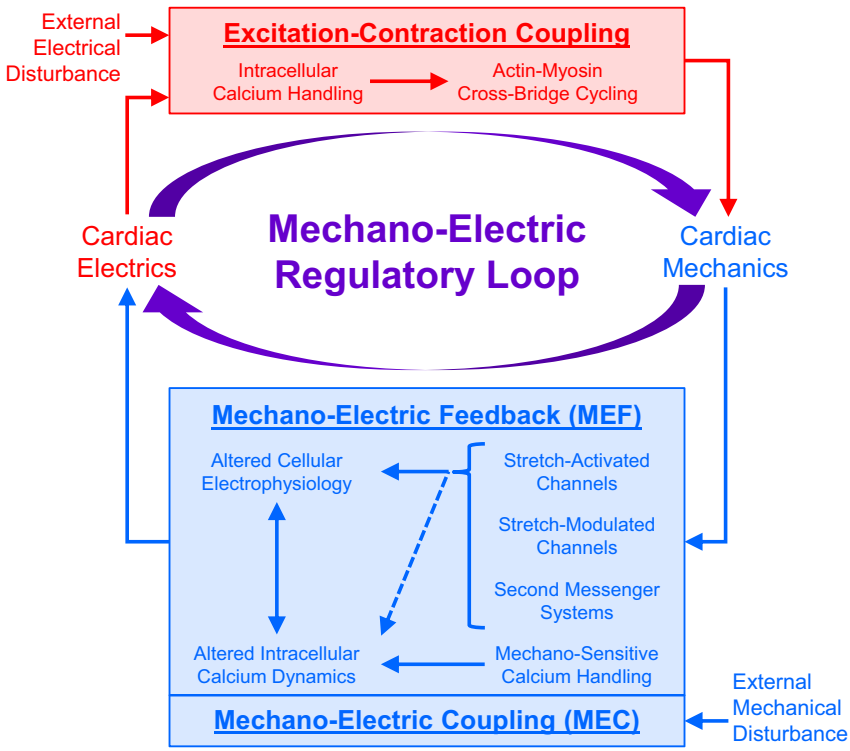


FIGURE 1. The feedforward and feedback links between cardiac electrophysiology and mechanics, forming the intracardiac mechano-electric regulatory loop. The feedforward between electrical excitation and mechanical contraction, involving intracellular calcium (Ca^{2+}) handling and actin-myosin cross-bridge cycling, is a process known as "excitation-contraction coupling." Feedback 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" (which, strictly, would consider only cardiac mechanical activity as an input signal) or more broadly "mechano-electric coupling" (which encompasses mechanical perturbations of the heart irrespective of their origin). [Adapted from Quinn (487), with permission from Springer Nature.]

chanical stimulus), stretch-modulated ion channels (whose primary mechanism of activation is non-mechanical, but whose activity is modulated, usually increased, by mechanical stimulation), changes in calcium handling, and second messenger systems, have far-ranging physiological effects on the heart, from altered electrophysiological properties including excitability, refractoriness, and electrical load, to changes in heart rate (HR) and rhythm, AP shape, and electrical conduction. These effects have important clinical consequences, including the induction or termination of arrhythmias.

In this review, following a brief look at the history of MEC research, we will present the evidence for and implications of MEC in humans; summarize insight into MEC effects that have been gleaned from whole animal, organ, tissue, and cell studies; explore potential molecular mechanisms of MEC; and reflect upon the utility of integration of mechano-electric interaction data by computational modeling.

B. Brief History of MEC Research

Early case reports on mechanically induced changes in heart rhythm date back, in the European medical literature, at least to the late 19th century [e.g., on mechanically induced sudden death by Felice Meola (394), Auguste Nelaton (426), and Ferdinand Riedinger (519)]. At the turn of the 20th century, systematic experimental studies in whole animals explored phenomena ranging from commotio cordis [e.g., Georg Schlomka (543)] to stretch-induced increase in HR (23). Mechanistic insight from AP recordings in isolated cardiac tissue started to emerge in the 1960s, when Klaus Deck characterized the stretch-induced positive chronotropic response in isolated SAN from rabbit and cat (147). These intracardiac, mechanically induced electrophysiological effects (discussed in sect. II*A*) were first recognized as an expression of mechano-electric feedback ("*Mechano-Elektrische Rückkoppelung*") in a paper by Raimund Kaufmann and Ursula Ravens (née Theophile) that reported a stretch-induced increase in automaticity of Purkinje fibers from rhesus monkeys (292).

Stretch-induced electrophysiological effects in working myocardium (e.g., acceleration of early repolarization, depolarization in later phases of the AP, and the potential of triggering ectopic beats) were demonstrated in the frog by Max Lab in the 1970s (329). Ten years later, Michael Franz et al. (180) showed that an acute increase in intraventricular volume in hearts from dogs caused diastolic depolarization that could be used to pace the asystolic heart. Around the same time, direct evidence for the presence of MEC in human ventricles came from Peter Taggart et al. (593), who reported an acute decrease in AP duration upon increased left ventricular pressure in patients being weaned from cardiopulmonary bypass, and Joseph Levine et al. (347), who showed similar results during acute right ventricular outflow tract occlusion in patients undergoing balloon valvuloplasty (these observations are discussed in sect. II*B*). Another 10 years later, similar MEC responses were shown to exist in the atria by Flavia Ravelli and Maurits Allessie (507) (described in sect. II*C6*).

Molecular MEC mechanisms started to emerge in 1984, with single-channel recordings of currents through SAC in cultured embryonic chick skeletal muscle by Falguni Guharay and Frederick Sachs (209). This was followed soon after by recordings of SAC currents in rat isolated ventricular myocytes (133; discussed in sect. II*A*), and later by cloning of SAC ion channels (accomplished in *Escherichia coli*; Ref. 580) and structural analysis using X-ray crystallography (99). At the tissue and whole heart level, investigations of the role of SAC currents in observed MEC responses have involved the use of pharmacological blockers (described in sect. III), while the structural homologue to the bacterial SAC in the mammalian heart remains unknown (a particular focus of recent research has been on determining its molecular identity). At the same time, significant attention has been paid to non-sarcolemmal mediators of MEC, particularly stretch-effects on intracellular calcium (Ca^{2+}) handling (described in III*B3*).

Importantly, the experimental innovations mentioned above have been complemented by rapid advancement of computational modeling, which has enabled the integration and interpretation of data, and the generation of novel, experimentally testable hypotheses (312, 493, 616) (described in sect. IV). Thus, building from a strong history, the present and future of MEC presents exciting possibilities, as is elucidated below.

II. PHYSIOLOGICAL AND CLINICAL RELEVANCE OF MEC

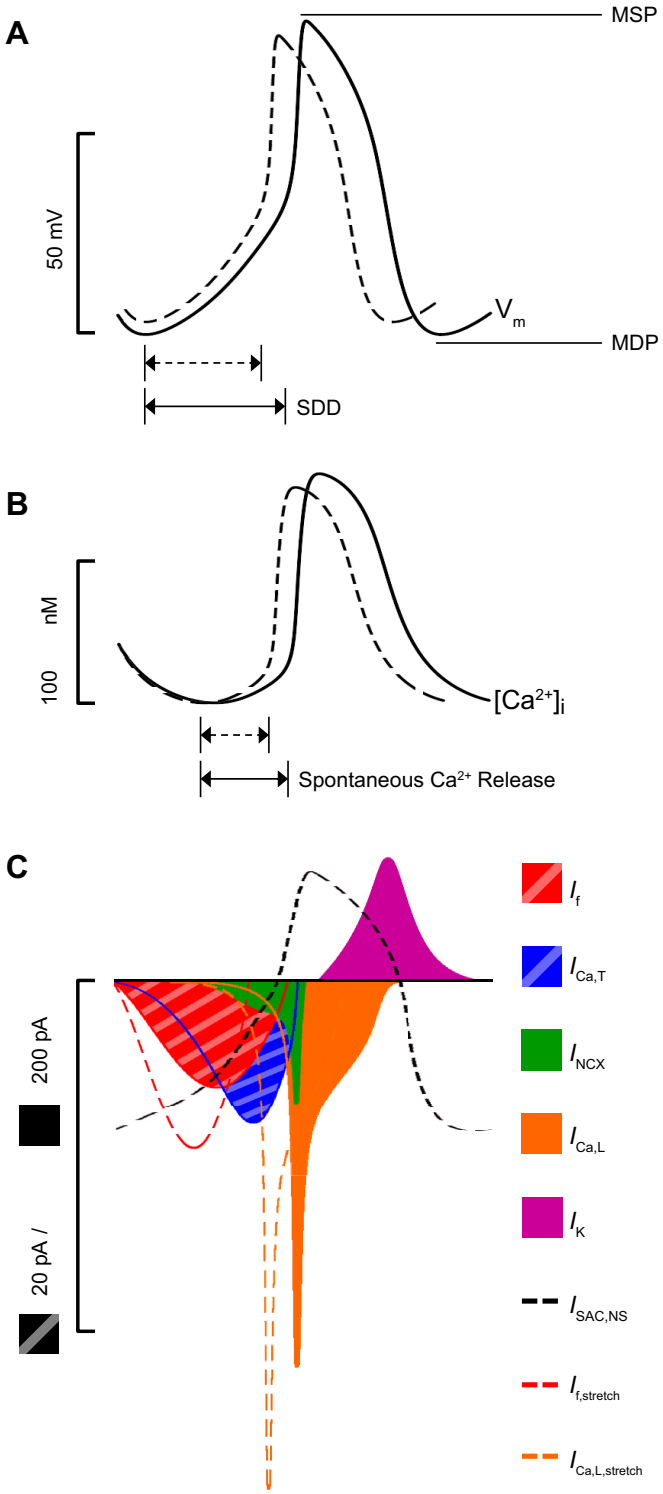
A. Modulation of Heart Rate

1. Mechanisms of SAN automaticity

The perhaps clearest example of a physiological role for MEC is the response of the heart's primary intrinsic pacemaker to stretch (23, 147). Normal excitation of the heart originates from the SAN, a tissue region located in the wall of the right atrium that displays spontaneous rhythmic excitation (295). At the whole cell level, SAN electrophysiology has been well described (269): rhythmic SAN firing requires spontaneous diastolic depolarization of the transmembrane potential (V_m) from its most negative value (maximum diastolic potential) towards threshold for AP firing (illustrated in **FIGURE 2*A***).

Early spontaneous diastolic depolarization is driven by a depolarizing inward current through hyperpolarization-activated cyclic nucleotide-gated channels ("funny" current,

I_f) and background conductances [e.g., for Na^+ concentration, $I_{b,Na}$ (438)], facilitated by a continual reduction in repolarizing outward potassium (K^+) currents (152). As diastole progresses, spontaneous diastolic depolarization rate increases by activation of inward Ca^{2+} flux through voltage-gated "transient" Ca^{2+} channels ($Ca_V3.1$ carrying $I_{Ca,T}$) and, upon further depolarization, long-lasting Ca^{2+} channels ($Ca_V1.2/1.3$ carrying $I_{Ca,L}$), whose activation ultimately drives the AP upstroke in SAN cells of large mammals (395) [in mice, fast Na^+ channels carrying I_{Na} also contribute to SAN AP upstroke (342), affecting the translational utility of mice for studies into SAN electrical function]. This system of membrane-bound ion channels can independently give rise to cyclic spontaneous AP generation, as illustrated by quantitative computational models (680). This cardiac pacemaker mechanism has been referred to as a "voltage clock" [V_m clock (380); summarized, along with potential stretch effects, in **FIGURE 2*C***].



Spontaneous diastolic depolarization of SAN cells is also facilitated by Ca^{2+} release from the sarcoplasmic reticulum (SR), occurring either spontaneously or triggered by Ca^{2+}-induced Ca^{2+} release upon activation of $I_{Ca,L}$ (612). Cytosolic Ca^{2+}, extruded from the cell by the Na^+-Ca^{2+} exchanger (I_{NCX}), gives rise to membrane depolarization, as I_{NCX} is "electrogenic" in that it moves three Na^+ ions into the cell for each Ca^{2+} ion removed. As SR Ca^{2+} release remains rhythmic for a period of time, even in the absence of cyclic changes in V_m, this electrogenic effect is also sufficient to drive SAN pacemaking (335), and it has been referred to as the "Ca^{2+} clock" of cardiac pacemaking (380) (summarized, along with potential stretch effects, in **FIGURE 2, *B* AND *C***).

When considering mechanisms that drive pacemaker activity, it is important to remember that pacemaker function adapts to changes in hemodynamic load on a beat-by-beat basis. The V_m and Ca^{2+} "clocks" do not inherently account for this rapid response to circulatory demand (cellular Ca^{2+} balance changes over multiple beats, while mechanically driven variation of sarcolemmal ion channel expression takes even longer). Thus another set of mechanisms, sensitive to the SAN's cyclically changing mechanical environment, must contribute to spontaneous diastolic depolarization. In analogy to the above terminology, this may be considered a "mechanics-clock" (496, 622). Of course, the concept of multiple "clocks" providing one "time" (initiation of each heartbeat) is somewhat counterintuitive: if one

FIGURE 2. The coupled voltage (V_m)/calcium (Ca^{2+})-oscillator system in sinoatrial node (SAN) cells and its modulation by the mechanical environment. *A* and *B*: SAN V_m (*A*) and intracellular calcium concentration ($[Ca^{2+}]_i$, *B*) under normal conditions (solid line) and during stretch (dashed line). Time intervals of spontaneous diastolic depolarization (SDD) and spontaneous Ca^{2+} release are indicated; note that SDD largely overlaps with the period of maximal mechanical distension of the SAN in situ. MSP, maximum systolic potential; MDP, maximum diastolic potential. *C*: transmembrane ionic currents associated with the V_m/Ca^{2+}-oscillator system. Shaded currents ["funny" current (I_f), transient calcium current ($I_{Ca,T}$)] and the cation-nonselective stretch-activated current ($I_{SAC,NS}$) refer to the 20 pA scale, solidly filled current plots [sodium-calcium exchanger current (I_{NCX}), long-lasting calcium current ($I_{Ca,L}$), delayed rectifier potassium current (I_K)] refer to the 200 pA scale, and dashed lines refer to theoretical changes with stretch. [Adapted from Quinn and Kohl (496), with permission from Elsevier.]

considers SAN activation as the uniform "time" output, then the various underlying mechanisms would better be conceptualized as a system of three coupled oscillators.

Pacemaker electrophysiology has been studied largely in isolated, mechanically unloaded cells. In vivo, the SAN is subjected to cyclic yet variable changes in its mechanical environment. During atrial diastole, the SAN is stretched by the downward shift of the atrioventricular valve-plane during ventricular contraction (214) and the associated filling by venous return. Peak stretch levels coincide with spontaneous diastolic depolarization, which is affected by stretch-induced inward currents (120) (discussed further in sect. III), thus "mechanically priming" SAN cells during the very period when their V_m moves towards threshold for excitation.

The contribution of mechanical load to spontaneous diastolic depolarization and SAN excitation timing was established in 1964, when Klaus Deck reported microelectrode recordings of V_m during equi-biaxial stretch of cat and rabbit isolated SAN tissue, demonstrating an increase in spontaneous diastolic depolarization and spontaneous beating rates (147). The critical nature of the mechanical environment for spontaneous, rhythmic SAN excitation was confirmed soon after, as it was shown that slack isolated SAN tissue often shows no, or irregular, excitation, while moderate stretch restores rhythmic pacemaker activity in previously quiescent or arrhythmic SAN tissue (73, 337) **(FIGURE 3)**. Preload may in fact be critical to SAN pacemaker activity from the very first heartbeat during embryonic development (e.g., day 22 in the human embryo), as physiological loading (fluid pressure build-up in the quiescent cardiac tube) may be a prerequirement for initiation and preneuronal control of cardiac excitation during ontogenesis (104, 504, 505).

Ultimately, through the combined actions of the various pacemaking oscillators, spontaneous diastolic depolarization causes V_m to cross the activation threshold for AP generation, resulting in the initiation and spread of a new wave of cardiac excitation (395). While the roles and interrelation of the mechanisms of SAN automaticity are still debated [V_m, Ca^{2+}, and mechanics oscillators can, in the experimental setting, each independently induce SAN excitation (153, 379, 525)], they represent overlapping and redundant systems that do not operate in isolation. Their interplay supports a robust and flexible system that integrates multiple functionally relevant inputs to provide a reliable basis for cardiac rhythmicity (259).

2. SAN mechano-sensitivity

SAN automaticity is influenced by extrinsic cues, such as biochemical signals from the autonomic nervous system and circulating hormones (374), as well as biophysical factors including preload. Mechano-sensitivity of SAN pacemaking was first established in the laboratory of Albert von Bezold, who reported sinus tachycardia induced by an increase in venous return in rabbits in whom the heart's sympathetic and parasympathetic connections with the nervous system had been cut ("denervated") (570). More generally known is the work by Francis Bainbridge, who demonstrated that right-atrial distension by intravenous fluid injection in anesthetized dogs causes an increase in HR (23), a response now known as the "Bainbridge effect."

Demonstrating that the Bainbridge effect also occurs in humans was difficult, as most noninvasive interventions that raise central venous pressure (such as tilt-table studies) tend to also increase arterial pressure and trigger the (dominant) baroreceptor-mediated depressor reflex. It was not until 1978 that David Donald and John Shepherd overcame this challenge by passively elevating the legs of volunteers in the supine position (155), which raised central venous pressure (by favoring venous return) without a simultaneous rise in arterial pressure. This resulted in an increase in HR that unequivocally established the presence of a positive chronotropic response to stretch in humans.

Under most conditions, the degree of filling of the right atrium, and thus the extent of stretch of the SAN, is primarily determined by venous return. Venous return is modu-

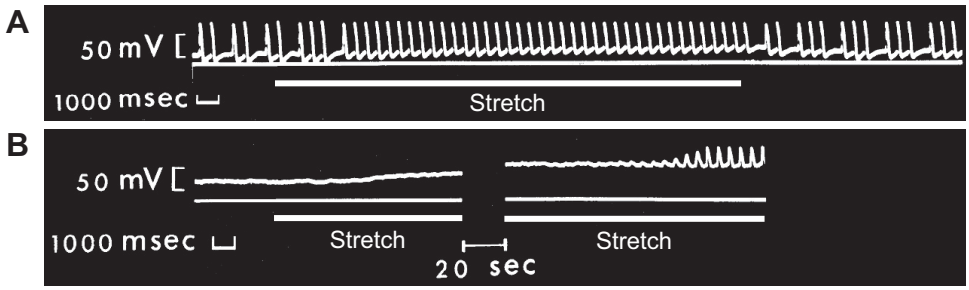


FIGURE 3. Effects of stretch on isolated sinoatrial node beating rate. Floating microelectrode recordings of transmembrane potential in cat isolated sinoatrial node, showing a stretch-induced shift of the maximum diastolic potential towards less negative values, resulting in restoration of regular rhythm in a preparation with irregular activity at slack length (*A*), or initiation of spontaneous excitation in a previously quiescent preparation (*B*). In both examples, tissue length was increased by ~40% from slack, with periods of stretch indicated by the lower horizontal lines. [Adapted from Lange et al. (337).]

lated, for example, by breathing, posture, physical activity, and vascular tone. Through the Bainbridge effect, HR in large mammals is raised in response to an increase in right atrial filling. Along with cell length-dependent changes in stroke volume (a consequence of the Frank-Starling Law–for further discussion of mechano-mechanical coupling, see Refs. 81, 428, 497), this stretch-induced response helps match cardiac output (HR × stroke volume) to changes in venous return. The Bainbridge effect also opposes the baroreceptor response [the Bezold-Jarisch or depressor reflex, which reduces HR when arterial blood pressure is increased (271, 636)], thus preventing excessive slowing of beating rate or diastolic (over-)distension of the right atrium, while maintaining cardiac output and adequate circulation during hemodynamic changes that increase both venous return and arterial pressure. Interestingly, a response similar to the Bainbridge effect may also occur in cells of the lower order pacemaker and conduction system, where Purkinje fibers, stretched during ventricular diastole (91), show a mechanically induced increase in automaticity (292, 536) and conduction velocity (146, 154, 524).

The fundamental importance of SAN mechano-sensitivity is indicated by its presence across the invertebrate (546) and vertebrate phyla (464). Originally assumed to be a neurally mediated reflex (the near-instantaneous response suggests that circulating humoral factors are not responsible), it can be observed not only in intact animals, but also in isolated hearts, tissue, and single pacemaker cells, indicating that intracardiac mechanisms are indeed key contributors (489, 496).

Ex vivo evidence has added further support to the notion of a nervous system-independent mechanism for the stretch-induced increase in HR, as the chronotropic response to stretch is insensitive to ablation of intracardiac neurons (663) and pharmacological block of Na^+ channels (103, 663) or adrenergic and cholinergic receptors (30, 52, 61, 72, 73, 103, 337, 465, 663).

There is evidence, however, for an interaction between mechanical and autonomic HR modulation. Stretch causes both an increase in HR and a decrease in the response to vagus nerve stimulation in whole animals (62) and isolated tissue (664). Conversely, when HR is reduced by vagus nerve stimulation, the stretch-induced increase in HR is enhanced (61, 72, 664), possibly in part through stretch-inactivation of the stretch-modulated acetylcholine-activated K^+ current (219). The stretch response is similarly enhanced when HR is first reduced by pharmacological parasympathetic or cholinergic stimulation, and diminished when HR is increased by adrenergic stimulation (30, 60, 72, 147, 219, 527, 664). In the case of excessive adrenergic stimulation, the direction of stretch-induced changes in HR may reverse [i.e., give rise to slowing (30)], similar to the response seen in mouse [a species with an inherently high HR (119), limiting the utility of mice for translational studies of cardiac MEC responses]. Yet, whether these changes in chronotropic stretch-responses are driven by an interaction of intrinsic (stretch) and extrinsic (autonomic nervous system) effects, or simply result from HR-dependent differences in the electrophysiological response to stretch, is difficult to tell [several studies have reported that the positive chronotropic response to stretch is enhanced at lower HR, regardless of the nature of the HR reduction (113, 119)].

Combined actions of stretch- and neuronally mediated effects on HR are evident also from variations in HR that are synchronous with the respiratory cycle: HR rises during inspiration and declines during expiration. This phenomenon, noted in humans more than 170 years ago by Carl Ludwig (372) and referred to as "respiratory sinus arrhythmia" (even though it is a physiological fluctuation in heart rhythm, not an arrhythmia per se) has long been considered to be a consequence–and, hence, useful clinical indicator–of "vagal tone." Yet, respiratory sinus arrhythmia continues to exist, albeit at a reduced magnitude, in the transplanted (i.e., denervated) human heart (44, 45, 502), during autonomic block (558, 569), and in acutely vagotomized animals (472), indicating a contribution of intrinsic, mechanically-mediated mechanisms.

The MEC contribution to respiratory sinus arrhythmia is driven by fluctuations in right atrial volume during respiration, as venous return is favored–by reduced intrathoracic and increased abdominal pressure–during inspiration, and impeded during expiration. During physical activity, non-neuronal responses appear to become the sole driver respiratory sinus arrhythmia-mediated fluctuations in HR even in healthy volunteers, as cyclic fluctuations in venous return are increased with increased respiratory effort, while "vagal tone" is reduced during physical activity (45, 95). In keeping with this, during positive pressure ventilation, which reverses the thoraco-abdominal pressure gradients relative to the respiratory cycle, respiratory sinus arrhythmia can switch phase so that HR decreases during inspiration, as intrathoracic positive pressure application impedes venous return to the heart below levels present during passive expiration (370).

3. SAN dysfunction

Mechanical modulation of HR appears to be functional only within a certain range of mechanical loads, as excessive stretch can result in irregular rhythms (337) and multifocal activity (234). This may be relevant in cardiac pathologies associated with atrial volume overload (417, 535, 565), where naturally occurring HR variability is reduced by SAN stretch (240, 391), an adverse prognostic marker. Decreased SAN distension upon increased myocardial stiffness, resulting from cardiac fibrosis or structural remodeling in advanced age (410, 530), atrial fibrillation (AF) (170, 325), or other cardiac pathologies (2, 53, 322, 421), may also contribute to SAN dysfunction, and may be further

exacerbated by mechano-sensitive non-myocytes (315, 317). The potential importance of age-related SAN remodeling for stretch-induced responses is supported by the greater increase in HR that occurs with similar stretch of the SAN from younger versus older animals (147).

Another important consideration in the context of SAN mechanics is the structural heterogeneity of the SAN, which results in regional differences in tissue stiffness and stretch (433). Changes in HR have been shown to correlate best with maximum SAN stretch, which occurs at its periphery, a region more distensible than the central node (279). This regional difference may be important for transmission of electrical activity from the SAN to atrium (195), as the SAN periphery is where (the possibly stretch-modulated) I_f is thought to play the largest role in SAN pacemaking. This is due, in part at least, to the more negative maximum diastolic potential in that region (caused by electrotonic influences from coupled working cardiomyocytes), which activates more I_f and increases the driving force for cation-nonselective stretch-activated channels (SAC_{NS}) (323, 431). These regional differences in SAN mechano-sensitivity may be exasperated by heterogeneous changes in SAN mechanical properties, or by variable expression and activity of SAC and stretch-modulated ion channels during disease or aging (65, 575, 600).

It is important to note, however, that it is not entirely clear what constitutes a normal or a pathophysiologically-altered SAN mechanical environment. In this context, questions that should be explored in further research include: whether the key mechanical parameter for changes in SAN function is stretch (279, 536), stress (14, 73, 103), or a combination of both (337); whether the rate of change in mechanical load affects SAN electrophysiology (73, 337) or not (103); and whether certain spatial loading patterns (e.g., linear, equi-biaxial, multi-axial) are more appropriate than others (147). Additionally, as mechanical responses, at least in ventricular myocytes, are AP shape- and phase-dependent (86, 181, 222, 437), the timing of mechanical stimulation is an important variable that may be affected by disease. This could help to explain species differences in the chronotropic response to stretch [i.e., mouse vs. larger mammals (119), as discussed further in sect. III*A1*].

4. Summary

The SAN, the heart's intrinsic pacemaker, initiates the heartbeat. Its rate of firing is determined by the interaction of multiple oscillators (V_m, Ca^{2+}, mechanics) whose integrated activity sets the clock for robust automaticity and regular heart rhythm. The chronotropic response to SAN stretch (Bainbridge effect) allows HR to be tuned to hemodynamic demand on a beat-by-beat basis, governed by effects intrinsic to SAN pacemaker cells. Abnormal stretch can result in a disturbance of rhythm, representing a potential contributor to SAN dysfunction with age and in disease. While much is understood about SAN function and its control by the mechanical environment, most ex vivo studies are performed in unloaded preparations, leaving questions regarding the (patho)physiological importance of MEC in the SAN unanswered, thus warranting further investigation.

B. Transient Effects on Whole Heart Electrical Activity

1. Diastolic stretch

Electrophysiological effects of acute mechanical stimulation are cardiac electrical cycle-dependent. In "electrical diastole" (here used to describe the period when cells of the working myocardium are at their resting V_m), a sufficiently large mechanical stimulus will cause depolarization, in a stretch-amplitude dependent manner. If supra-threshold, this can trigger excitation in whole heart **(FIGURE 4*A*)**, tissue, and cells (495). In the whole heart, this is true both for transient increases in intraventricular volume (54, 150, 151, 161, 180, 181, 221–223, 245, 301, 424, 459, 460, 513, 547, 568, 650, 688) and for local tissue deformation, such as upon contact of intracardiac devices (e.g., the tips of catheters or pacing leads) with the endocardium (35) or by epicardial and precordial impact (71, 492, 494) **(FIGURE 4*B*)**. Interestingly, both for global and local mechanical stimuli it appears that depolarization depends on tissue stretch, rather than stress. With an increase in intraventricular volume, the amount of volume required for excitation is remarkably consistent between hearts of the same species, while the associated change in intraventricular pressure shows high variability (222), depending on the speed of volume changes applied [in contrast, stretch-induced changes in refractoriness have been shown to correlate best with ventricular wall stress (215)]. With local impact-induced tissue deformation, the extent of tissue indentation needed for excitation is similar between subjects and for various regions in a given heart, while the pressure under the probe can be highly variable (117, 492), depending on probe contact surface area and impact location. Depolarization also appears to depend on the rate of stretch application (320), which increases the magnitude of stretch needed to cause excitation at lower deformation rates (172, 181). This application rate dependence may be a consequence of myocardial visco-elasticity, where faster application of an external mechanical stimulus will be associated with a larger transient overshoot in local peak stretch levels, while slow application of a mechanical stimulus may cause mild depolarization and partial inactivation of I_{Na} [in keeping with experimental observations showing that the threshold for electrical stimulation is also affected by stretch dynamics, being reduced due to stretch-induced V_m depolarization (620)].

It should be noted that in the setting of a "global" stimulus, such as an increase in intraventricular volume, there will be spatially heterogeneous mechanical effects. Myocardial stiffness varies regionally throughout the heart,

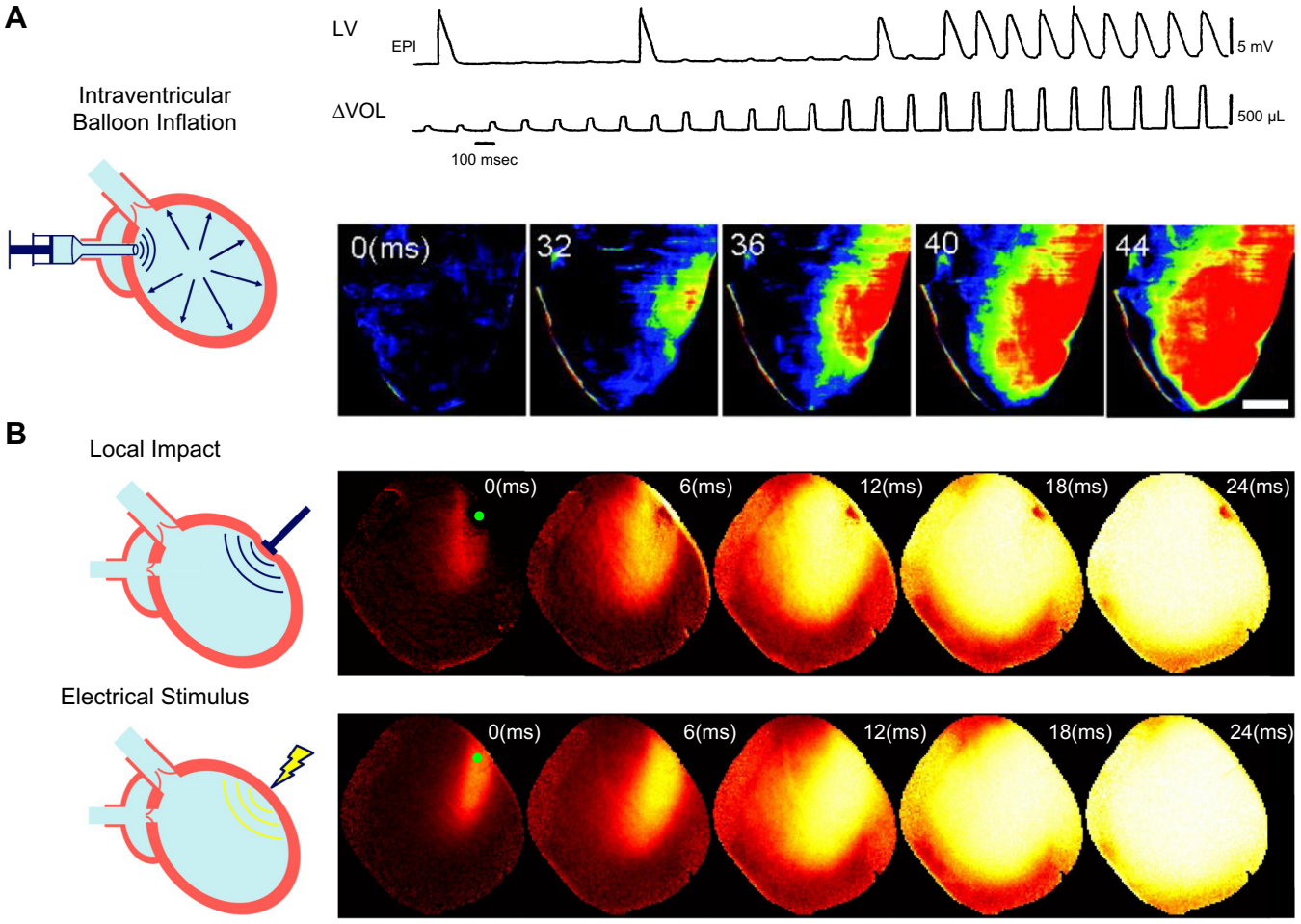


FIGURE 4. Mechanically induced excitation upon diastolic stimulation of rabbit isolated whole heart. *A, top row*: monophasic action potential recording from the left ventricular (LV) epicardium (EPI; top trace) during intraventricular volume pulses (ΔVOL; bottom trace) by inflation of an intraventricular balloon (schematic on left) during complete heart block, showing transient membrane depolarizations upon each balloon inflation whose amplitude increases with pulse volume; above a certain amplitude, each LV balloon inflation causes LV excitation (note: first two action potentials are spontaneous "escape beats" of the preparation). [Adapted from Franz et al. (181), with permission from Wolters Kluwer Health.] *A, bottom row*: optical mapping of right ventricle near-epicardial membrane potential showing focal excitation at the site of maximum stretch during an intraventricular volume pulse (scale bar = 4 mm). [Adapted from Seo et al. (547), with permission from Wolters Kluwer Health.] *B, top row*: optical mapping of LV near-epicardial membrane potential showing focal excitation resulting from a subcontusional local impact of the epicardium. *B, bottom row*: LV excitation pattern with an electrical stimulus applied to the same site as the local impact, showing a similar activation pattern downstream of the stimulation site (scale bar = 5 mm). [Adapted from Quinn et al. (492), with permission from Wolters Kluwer Health.]

resulting in nonuniform stretch and depolarization (101, 547). Upon global mechanical stimulation, excitation originates from areas where the largest stretch is observed, typically in the left ventricular free wall or the right ventricular outflow tract, depending on the cardiac chamber affected (101, 181, 547) **(FIGURE 4*A*)**. This again highlights the notion that stretch, not stress, is a main input signal for MEC.

2. Systolic stretch

When an increase in intraventricular volume is applied during "electrical systole" (i.e., during the AP), or maintained over the entire cardiac cycle, electrophysiological effects are generally characterized by a heterogeneous decrease in AP duration (APD) and refractoriness (54, 76, 86, 87, 101, 129, 130, 144, 161, 208, 215, 238, 331, 346, 511, 513, 514, 583, 642, 644, 688, 689), although some studies have reported an increase in both (40, 42, 131, 143, 655). These effects are also HR dependent (238, 511, 644) and generally thought to be accompanied by a decrease in tissue conduction velocity (150, 403, 554, 583, 655, 689), though an increase in conduction velocity has been seen in isolated ventricular tissue and engineered myocyte strands (252, 392). The stretch-induced decrease in conduction velocity has been attributed to effects on passive cable properties of

interconnected cardiomyocytes through an increase in axial tissue resistance (75), caused by an increase in sarcoplasm resistance (116, 652), as well as an increase in cardiomyocyte membrane capacitance caused by incorporation of subsarcolemmal caveolae into the cell surface membrane (311, 477). The reported discrepancies in electrophysiological responses to systolic or sustained stretch mentioned above (some of which came from the same groups) may relate to differences in species (e.g., small vs. large animal), preparation (e.g., intact animal vs. isolated heart or tissue or cell), physiological factors (e.g., baseline heart rate, AP morphology), experimental considerations (e.g., mechanical stimulus magnitude, measurement technique, temperature), or data handling (e.g., measurement algorithms).

Similar effects of acute changes in ventricular preload have been seen in humans (448). For instance, an increase in intraventricular volume upon discontinuation of cardiopulmonary bypass results in a heterogeneous decrease in APD (593). In contrast, however, acutely reducing intraventricular volume (over 15 s) by the Valsalva maneuver (which involves forced expiration against a closed glottis, causing an increase in intrathoracic pressure that impedes venous return) in patients undergoing routine cardiac catheterization procedures has been shown to also decrease APD, even in transplant recipients with denervated hearts, in whom a concomitant autonomic response is eliminated (590). This decrease in APD with reduced intraventricular volume has been suggested to relate to a reduction in myocardial shortening (rather than the change in intraventricular volume), as APD changes correlate with ventricular wall-motion changes (589). A similar decrease in APD occurs in experimental studies when myocardial shortening is restricted during isometric contraction (293, 329, 571). Naturally occurring oscillations in ventricular preload, much like for respiratory sinus arrhythmia in the SAN, may also cause respiratory-related (225, 625) and lower-frequency ("Mayer wave") fluctuations (224, 484) in ventricular repolarization.

An acute increase in ventricular afterload, on the other hand, for instance due to aortic constriction (449, 591) or pulmonary balloon valvuloplasty (347), also results in a heterogeneous decrease in APD, and can lead to afterdepolarization-induced ectopy (347). Ectopic excitation also occurs in experiments involving rapid increases in aortic blood pressure (550, 552, 553), potentially due to post-systolic myocardial deformation (212), which is reduced by antihypertensive treatment (551, 553). Conversely, an acute reduction in ventricular pressure overload, as occurs following balloon valvuloplasty or angioplasty, increases APD (347) (although this may partly reflect mechanically-induced afterdepolarization) and decreases dispersion of repolarization (538).

MEC may play a role in coordinating whole heart electrical activity by helping to generate homogeneity out of the complex, physiologically necessary electrophysiological and mechanical heterogeneity that exists at the cellular level across the heart (291). The interplay of regional mechanical effects of a contraction-induced intraventricular pressure wave and the phase of the AP in early and late activated regions may act to regionally synchronize ventricular repolarization (446, 486). A similar effect has been shown using duplexes of individually controlled, mechanically interacting (in-parallel or in-series) cardiac muscle segments that allow for the simulation of mechano-electric interactions in heterogeneous myocardium (382, 561). This experimental model has demonstrated that mechanical heterogeneity contributes differently to APD changes when muscle segments are coupled in-parallel or in-series, which may play a role in mechanical tuning of electrical activity in distant tissue regions. Also, the electromechanical activity of mechanically interacting contractile elements is affected by their activation sequence, which may optimize myocardial performance by reducing intrinsic APD differences. Pathophysiological, nonuniform ventricular contractions, on the other hand, can lead to electrocardiogram (ECG) T-wave vector displacement (563) and, along with increased intraventricular volume, may be partly responsible generation of the ECG U-wave (105, 124, 185, 542, 584–586).

3. Summary

Acute electrophysiological effects of MEC depend on the timing of mechanical stimulation relative to the AP cycle of affected cells. Mechanical stimulation, whether local or global, during electrical diastole will–if large enough to give rise to any change in electrophysiology–cause depolarization of V_m. This may trigger premature and/or ectopic excitation. If instead timed during the AP, or sustained over the entire cardiac cycle, mechanical stimulation affects APD, refractoriness, conduction, and the dispersion of those parameters across the heart, potentially causing a pathological increase in electrophysiological heterogeneity, while normally playing a physiological coordinating role. Even though these effects are well established, critical parameters determining MEC outcomes, such as the relative importance of stretch versus stress, the actual levels of stretch or stress experienced by individual cells within the tissue, the rate of mechanical stimulus application, and underlying mechanical and electrical heterogeneities are unclear, necessitating future research.

C. Induction of Sustained Arrhythmias

1. Tissue-level mechanisms of stretch-induced arrhythmias

As mentioned in section II*B1*, diastolic mechanical stimulation may cause depolarization and trigger excitation (**FIG-**

URE 5A). While extra beats in healthy heart will mostly have benign consequences, ectopic excitation accompanied by mechanically-induced effects on electrophysiological tissue properties during an AP can interact with underlying electrical activity to cause severe tachyarrhythmias (487).

Ventricular tachyarrhythmias are thought to arise as a result of untoward interactions of an arrhythmogenic trigger and a substrate for reentry (699). Both of these may be favored by, or result from, MEC effects (268, 330, 510). Across the heart, electrical systole involves dispersion of V_m, as cells in atria and ventricles depolarize (P- and QRS-waves of the ECG) and repolarize sequentially (atrial repolarization is not normally discernible on the ECG, ventricular repolarization is reflected by the T-wave). This gives rise to electrical tissue gradients that are relatively short upon activation, and more drawn-out upon repolarization, as witnessed for ventricles by the broad and smaller-amplitude ECG T-wave, compared with the QRS complex. As a result, mechanical stimuli during electrical systole tend to encounter locally differing stages of the underlying cellular AP, which–during repolarization–can furnish a substrate for re-entry, creating a vulnerable window for mechanically-induced ventricular tachyarrhythmia (FIGURE 5B).

Early studies of MEC, where intraventricular volume was acutely increased in ex vivo whole hearts, reported a decrease in the threshold for electrically induced excitation and tachyarrhythmias (including ventricular fibrillation, VF) (265, 513, 526); the same holds for AF inducibility during acute atrial dilatation (179, 506) (discussed in more detail in sect. IIC6). Also in isolated hearts, mechanically-induced excitation resulting from intraventricular volume pulses can trigger ventricular ectopy and tachyarrhythmias (54, 222, 547, 568). In vivo, an acute increase in intraven-

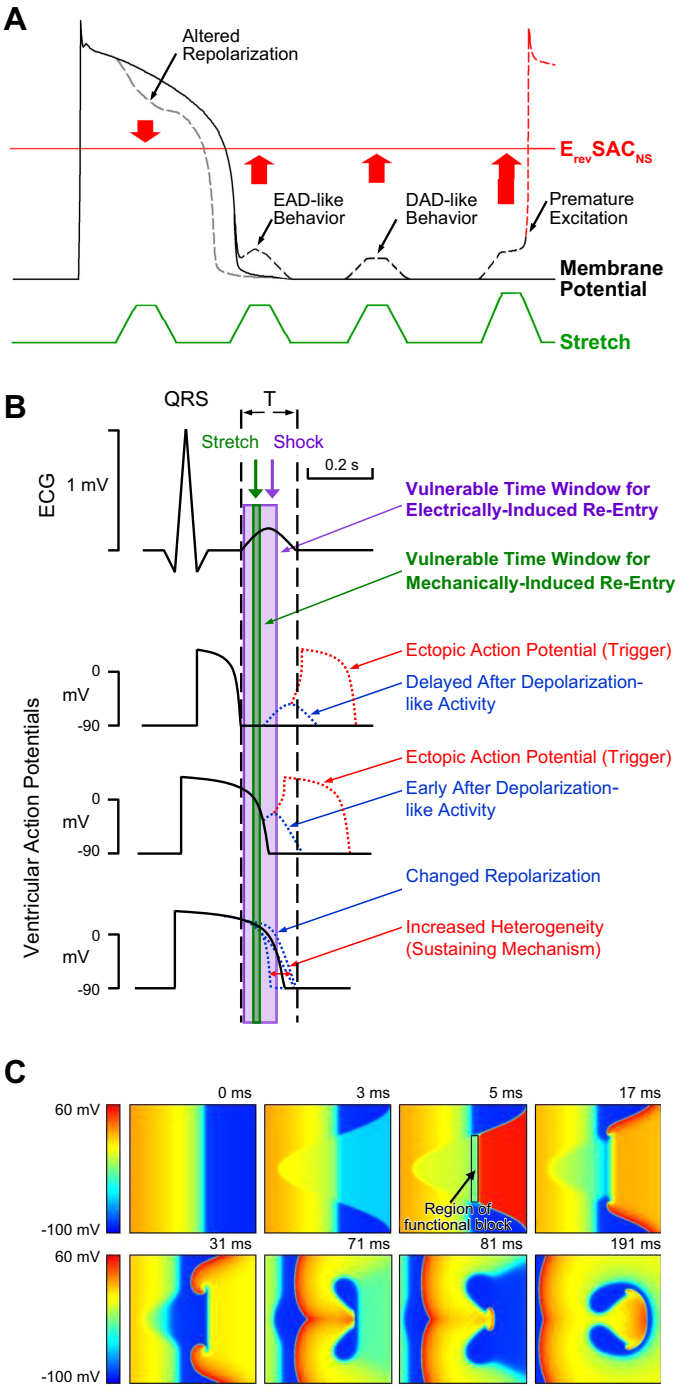


FIGURE 5. Mechanisms of stretch-induced arrhythmogenesis. *A*: schematic illustration of the effects of stretch (green line) on the transmembrane potential of ventricular myocytes (solid black line). Depending on stretch timing, the action potential may be shortened (gray dashed line), or the cell membrane may be depolarized (black dashed line), resulting in early (EAD) or delayed (DAD) after-depolarization-like behavior. If stretch levels are sufficiently large, premature excitation may be induced (red dashed line). The solid red line indicates the reversal potential (E_{rev}) of cation-nonselective stretch-activated channels (SAC_{NS}), towards which the membrane potential will be drawn upon SAC_{NS} opening. [Adapted from Kohl (308), with permission from Elsevier.] *B*: effects of stretch in the vulnerable window for mechanical stimulation (green bar) during the electrocardiogram (ECG) T-wave in the whole heart (the vulnerable window for electrical stimulation of the whole heart is shown for comparison of their duration, purple bar). Responses to mechanical stimulation vary regionally, depending on the local polarization state of the action potential, including DAD-like behavior in fully repolarized cells, EAD-like behavior in cells that are still repolarizing (which can result in premature excitation, i.e., arrhythmic triggers), or altered action potential duration in cells that are still near action potential plateau levels (which may increase electrical heterogeneity, i.e., an arrhythmic substrate). [Adapted from Kohl et al. (316), with permission from Oxford University Press.] *C*: computer simulation of mechanically induced sustained re-entry in a two-dimensional model of ventricular tissue. Only those mechanical stimuli (applied to the right "epicardial" edge of the model) that are suprathreshold (i.e., trigger an action potential) and overlap with a trailing repolarization-wave (previous action potential receding from right to left) cause sustained "figure-of-eight" re-entry, which occurs around the region of functional block (black rectangle), which is present at the intersection of "old" and "new" excitation waves. Membrane potential is color-coded; see scale bars. [Adapted from Garny and Kohl (194), with permission from John Wiley and Sons.]

tricular volume in experimental preparations (101, 180, 208), in patients during balloon valvuloplasty (347), or as a consequence of mitral valve prolapse, stenosis, or insufficiency (31, 122, 348) is associated with a high incidence of arrhythmias. Outcomes are typically mechanical stimulus magnitude- and ECG timing-dependent and may in part result from heterogeneous stress-stretch patterns due to the spatio-temporal dissociation between a globally uniform stimulus and its regional effect. In the volume-overloaded ventricle, there may also be contributions of excessive Purkinje fiber stretch to arrhythmias, which has been suggested to contribute to reduced conduction velocity (524) or loss of AP conduction (158, 292), subthreshold afterdepolarizations (175) and ectopic excitation (158, 234, 557), or rapid firing-induced tachycardia (158, 515, 608).

Similarly, local mechanical stimulation can result not only in ectopic excitation, but also in ventricular tachyarrhythmias, as reported upon tissue contact of central venous and pulmonary artery catheter tips (140, 169, 176, 251, 326, 340, 567, 577) or intracardiac catheters and electrodes (58, 339, 359, 398). The same is true for extra-corporeal mechanical stimuli, such as chest compressions during cardiopulmonary resuscitation (43), or impacts to the precordium (97) for instance in the setting of noncontusional mechanical stimuli causing commotio cordis **(FIGURE 6*A*)** (316, 385, 427).

2. Commotio cordis

Commotio cordis may be the most dramatic example of the consequences of mechanically-induced ventricular tachyarrhythmias, having been reported to result in VF-related sudden death at least as far back as the 1870s (394, 426). Even though VF by commotio cordis is a rare event, it is one of the most common causes of sudden death in youth athletes in the United States (383). Electrophysiological outcomes of commotio cordis are determined by mechanical stimulus characteristics such as anatomical location and impact area, duration, and energy (363, 364, 543). Studies in pigs have characterized mechanical inducibility of VF as inversely related to impact area and duration, rising with projectile stiffness and occurring only when impact-induced ectopy occurs during a vulnerable window that exists during a 10- to 20-ms period immediately before the peak of the ECG T-wave (360, 361, 365, 383) **(FIGURE 6*B*)**. Results indicate the susceptibility to VF by commotio cordis is subject specific (8) and, as for the chronotropic effects of stretch on SAN rate, is not affected by autonomic block (576) or denervation (543).

Computational modeling has helped to explain how precordial impact in the vulnerable window may lead to VF. Two-dimensional (2D) and three-dimensional (3D) simulations have demonstrated that commotio cordis-induced VF should arise only when a suprathreshold mechanical stimulus occurs at the trailing edge of the preceding wave of excitation, so that the mechanically-induced premature excitation forms directly adjacent to tissue that is functionally refractory (still repolarizing). This results in the generation of both a trigger (ectopy, via SAC_{NS} in the model) and a substrate (conduction block) around which sustained reentry can occur (194, 355) (**FIGURE 5*C***; discussed further in sect. IV*B2*). Conceptually, this is similar to the vulnerable window for extracorporeal electrical stimulation, which was systematically studied since the 1930s (660), but whose duration is significantly larger (≥100 ms in large animals; Ref. 549) than that described for precordial impacts (365). The difference in the length of the two vulnerable windows is a consequence of the fact that repolarization is spatially heterogeneous across the ventricles. Therefore, the condition for overlap of mechanically-induced excitation with the trailing repolarization-wave will be met in different cardiac locations at different time points of the cardiac cycle, and at each of these locations for brief periods only. This means that the vulnerable window for mechanical VF induction is determined by space and time (as is also the case for point electrical stimulation).

This theoretical concept has been tested in ex vivo rabbit hearts (492), demonstrating that local epicardial stimulation causes focal excitation underneath the contact site **(FIGURE 4*B*)** (as seen with intracardiac mapping during extracorporeal impacts in the pig model of commotio cordis; Ref. 7) **(FIGURE 6*C*)**. As predicted by modeling, this ectopic excitation results in VF **(FIGURE 6*D*)** if, and only if, the stimulus overlaps with the trailing edge of repolarization from the preceding sinus beat (492) **(FIGURE 6*E*)**.

3. Acute regional ischemia

Mechanical heterogeneity is thought to contribute to the induction of arrhythmias in regional ischemia (267). In patients with myocardial ischemia, there is a strong correlation between the presence of regional wall motion abnormalities and arrhythmogenesis (84, 557). In the acute phase, a large proportion of ectopic beats originates from the ischemic border zone (123, 328) **(FIGURE 7*A*)**, an area of particularly high stretch due to "paradoxical segment lengthening" of the ischemically weakened myocardium during cardiac mechanical systole (189, 479, 533, 609, 626). Also, in ischemic hearts that develop VF, stretch magnitude is related to the timing of VF onset (232). Similarly, the end-diastolic length of the ischemic region is a strong predictor of VF (26, 27, 29). In acute regional ischemia, a contribution of MEC to arrhythmogenesis is further supported by an increase in the incidence of ectopic activity in isolated hearts with elevated left ventricular pre- and afterload (established by an intraventricular balloon, connected to a fluid-filled column with a clamp to control ejection resistance), compared with an unloaded ventricle **(FIGURE 7*B*)**. In addition, it has been shown that following a potentiated con-

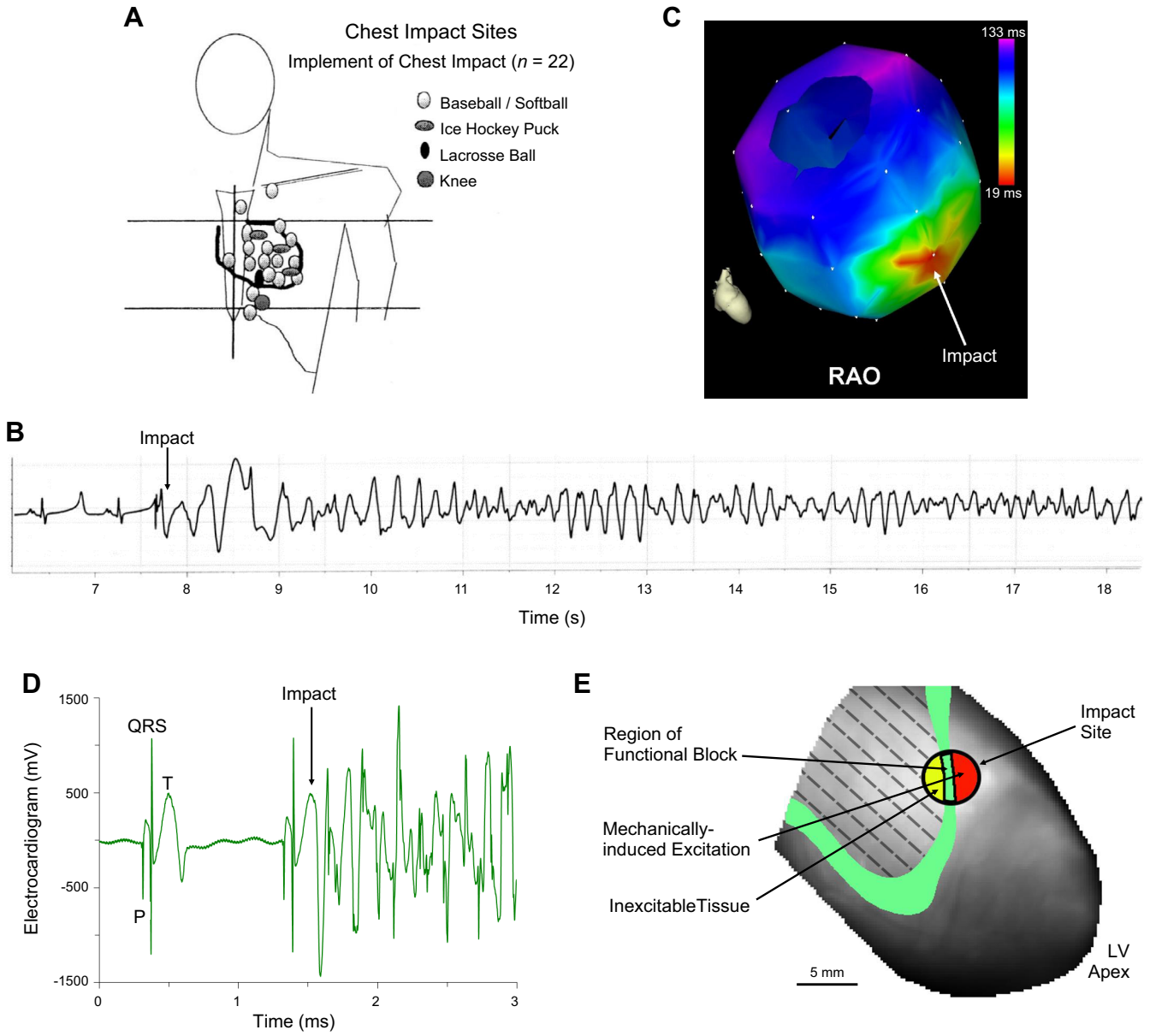


FIGURE 6. Mechanically induced ventricular fibrillation in the setting of commotio cordis. *A*: summary of location of lethal precordial impacts in victims of commotio cordis. [Adapted from Maron et al. (384), with permission from John Wiley and Sons.] *B*: electrocardiogram recording of instantaneous, impact-induced ventricular fibrillation in an anesthetized pig model of commotio cordis. [Adapted from Link (360), with permission from Wolters Kluwer Health.] *C*: global endocardial activation map [right anterior oblique (RAO) orientation] of impact-induced electrical excitation preceding ventricular fibrillation, highlighting the focal nature of the initial trigger event. [Adapted from Alsheikh-Ali et al. (7), with permission from Elsevier.] *D*: surface electrocardiogram from rabbit isolated heart showing the effect of local epicardial mechanical stimulation applied to the left ventricle (LV) during the early T-wave, resulting in instantaneous ventricular fibrillation. *E*: spatial interrelation of mechanical stimulation site and 50% repolarization isochrone of the preceding sinus beat, obtained from epicardial voltage mapping (green) in those cases where subcontusional mechanical stimulation did trigger ventricular fibrillation: only when mechanically induced excitation (red) occurs directly adjacent to still inexcitable tissue (yellow) is a region of functional block (black rectangle) formed, around which re-entry can occur (as predicted from computational modeling shown in **FIGURE 5*C***). [Adapted from Quinn et al. (492), with permission from Wolters Kluwer Health.]

traction due to an increased diastolic interval (which is presumed to increase stretch at the ischemic border), there is an increase in the likelihood of ectopic excitation (123), which is also seen after an increase in intraventricular volume (123, 459). These findings are supported by computational modeling that suggests mechanically-induced depolarization originating from the ischemic border zone (through SAC_{NS}) contributes to the formation of ectopic foci (if suprathreshold), or to the slowing and block of conduction (if subthreshold) (274) (**FIGURE 7*C***; discussed further in sect. IV*B2*).

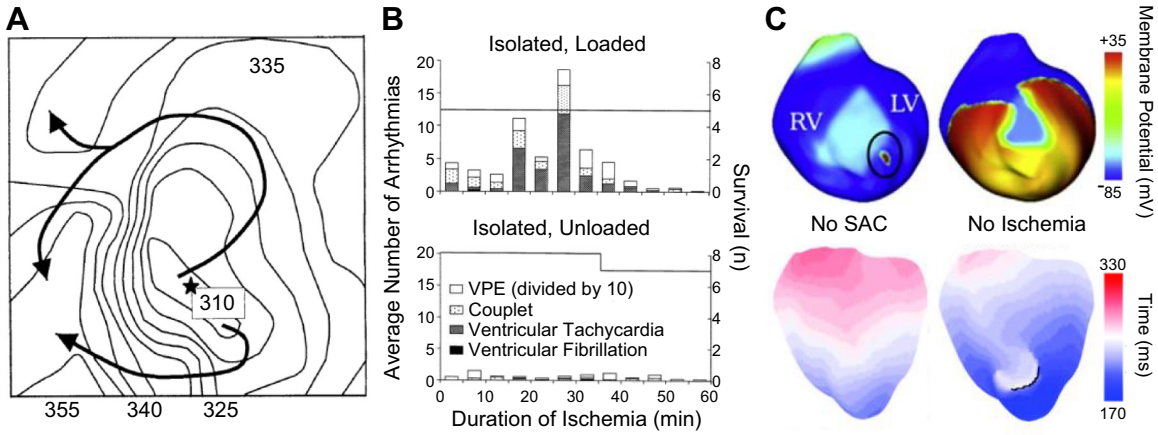


FIGURE 7. Mechanically induced arrhythmias during acute regional ischemia. *A*: activation map of ventricular premature excitation (VPE) originating at the ischemic border in a pig isolated heart model. *B*: plots summarizing greater frequency of arrhythmias in loaded versus unloaded pig hearts. [Adapted from Coronel et al. (123), with permission from Elsevier.] *C*: computational simulation of mechanically induced ventricular ectopy (black circle) and re-entry during acute regional ischemia (*top*) and simulated activation patterns without re-entry when omitting from the model either stretch-activated channels (SAC) or ischemic electrophysiological changes (*bottom*). [Adapted from Jie et al. (274), with permission from Wolters Kluwer Health.]

4. Mitral valve prolapse

Another pathological setting, in which regional changes in ventricular mechanics are thought to contribute to arrhythmogenesis, is mitral valve prolapse (31, 442). In mitral valve prolapse, one or both leaflets of the mitral valve bulge into the left atrium during ventricular systole, resulting in stretch of the leaflets, chordae tendinae, papillary muscles, and infero-basal ventricular wall (471). The resulting arrhythmias that occur in some patients involve complex premature ventricular excitation, arising from sites close to the anchor points of prolapsing leaflets and supporting structures, such as the papillary muscles, fascicular tissue, LV outflow tract, or mitral annulus, which can lead to sudden cardiac death (32). This excitation appears to occur due to mechanically-induced afterdepolarizations of tissue associated with the mitral valve (662) (particularly the papillary muscles; Refs. 186, 204, 248), by contact of the prolapsing leaflets snapping back against the ventricular myocardium during diastole (136), or by stretch of the valve itself (muscle fibers in the mitral valve leaflet have been shown to develop diastolic depolarization when stretched, potentially leading to automatic activity that may propagate into the surrounding myocardium; Ref. 668). The key role of abnormal mechanical forces is further supported by a series of cases in which surgical correction of bileaflet mitral valve prolapse resulted in a reduction of ventricular arrhythmias by relieving myocardial stretch (623).

5. Chronic pathophysiological states

In a host of chronic cardiovascular diseases, alterations in myocardial mechanical properties may contribute to electrophysiological changes that promote arrhythmogenesis. This had been initially proposed based on the observation that ventricular tachyarrhythmias are frequently encountered in pathologies associated with volume or pressure overload (327, 592). It is difficult, however, to identify causal relationships between tissue mechanics, MEC, and cardiac rhythm disturbances in chronic disease settings, as coinciding structural and functional remodeling, as well as fluctuations in metabolic and autonomic state, may be arrhythmogenic in their own right. Considering effects of acute changes in mechanical load, in particular the temporary removal of chronic overload, on ventricular electrophysiology in chronic pathophysiological states has been an alternative, yet effective way to elucidate the potential relevance of MEC in the induction and sustenance of ventricular arrhythmias.

One of the most striking examples is the anti-arrhythmic effect of an acute temporary decrease in intraventricular volume in patients suffering from chronic ventricular volume overload and tachyarrhythmias. In these patients, acute hemodynamic unloading (249), or a temporary reduction in cardiac chamber volume by the Valsalva maneuver (341, 648), rapid pacing (473), or repeated forceful coughs (651), can result in temporary termination of ventricular tachyarrhythmias (for as long as the reduced load is maintained) **(FIGURE 8)**, even in transplant recipients (10). In a similar vein, in patients with a dilated left atrium due to mitral stenosis, the associated arrhythmogenic dispersion and delays of conduction can be immediately reversed upon normalization of pressure gradients by percutaneous transvenous mitral balloon valvotomy (122).

In the opposite direction, an increased mechanical load on top of a chronic disease background can be pro-arrhythmic (587). For instance, in heart failure patients, average daily median pulmonary artery pressure has been

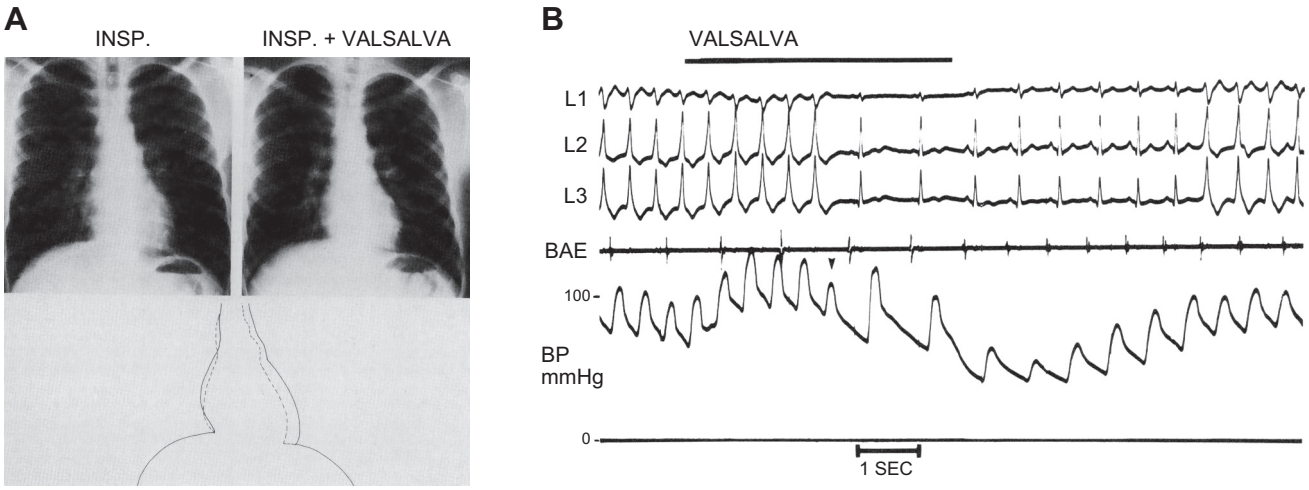


FIGURE 8. Temporary termination of ventricular tachyarrhythmia with acute hemodynamic unloading in human. *A*: X-ray images of the thoracic cavity of a patient in ventricular tachycardia after deep inspiration (INSP., *top left*) and after an identical inspiration followed by a strong Valsalva maneuver (*top right*, timing corresponding to label in *B*), with a tracing of the cardiac silhouettes below (solid line = INSP., dashed line = INSP.+VALSALVA). *B*: surface electrocardiogram leads 1, 2, 3 (L1–3), bipolar right atrial electrogram (BAE), and aortic blood pressure (BP) from the same patient showing as background activity atrioventricular dissociation and ventricular tachycardia. During the Valsalva maneuver, there is an initial increase in blood pressure (BP; corresponding to a period of blood redistribution away from the chest cavity, reducing heart size), followed by a decrease in BP, which is associated with a return to normal sinus rhythm. After the Valsalva maneuver is stopped, BP and cardiac volume return to control levels, and arrhythmia resumes. [From Waxman et al. (648), with permission from Wolters Kluwer Health.]

shown to correlate with the risk of ventricular tachyarrhythmias (512). In the setting of heart failure, acute increases in afterload occur on the background of pro-arrhythmic metabolic (mitochondrial oxidative capacity, fatty acid and glucose oxidation, rate of glycolysis), humoral (circulating catecholamines), electrophysiological (APD, conduction velocity, repolarization) and mechanical (structural remodeling, volume overload) changes, and it has been shown that an acute increase in intraventricular pressure alone may be as arrhythmogenic as the acidified catecholamine-rich milieu, or the electrical remodeling associated with heart failure (500).

Similarly, increased intraventricular preload may help in sustaining established ventricular tachyarrhythmias, as stretch accelerates activation and increases the complexity of ventricular tachyarrhythmias, potentially by producing more areas of transmural excitation breakthrough and/or conduction block (68, 106, 108–111, 413, 614). These effects can be eliminated by stabilizing ryanodine receptors (RyR) in their closed state (148), highlighting the crucial contributions of intracellular Ca^{2+} handling to MEC (discussed further in sect. III*B3*). Interestingly, an increase in intraventricular volume has also been shown to acutely reduce the effectiveness of antiarrhythmic drugs (514), while Na^+ channel block by flecainide may be potentiated by atrial distension (166).

In the case of ischemia, if infarction occurs, myocardium is replaced by stiffer scar tissue (518). The consequence is considerable mechanical heterogeneity (and stretch) at the infarct border zone (16), such that acute increases in intraventricular volume result in ventricular tachyarrhythmias, arising from the site of the largest stretch-induced change in repolarization (87). This effect of post-infarction mechanical heterogeneity on electrophysiology may be enhanced by mechano-sensitive non-myocytes in cardiac lesions, if electrically-coupled to surviving cardiomyocytes (317), and may explain why, in patients with myocardial infarction, acute afterload reduction can abolish arrhythmias (159, 419). Yet, little direct evidence exists regarding the role of MEC in post-infarction arrhythmias, and while mechanical heterogeneity does overlap with sites of arrhythmogenesis suggesting MEC could be involved, computational models have demonstrated that arrhythmias can arise from such regions without evoking MEC (15, 115, 393). Moreover, in the case of wall motion abnormalities, while non-uniform ventricular contraction is associated with increased dispersion of repolarization, dispersion appears to increase primarily in normally contracting regions of hearts that are not directly affected by the presence of infarction (447).

Potential contributions of MEC to arrhythmogenesis in chronic cardiac diseases may also be related to an increase in tissue mechano-sensitivity, as demonstrated in various animal models (272, 273, 281, 304, 485, 646). Chronic disease-related hypersensitivity of MEC may result from increased expression or sensitivity of SAC_{NS} current ($I_{SAC,NS}$; Ref. 281); increased microtubule density (460), altered viscoelastic properties (646), and a reduced com-

pensatory response to increased load (345); or altered intracellular Ca^{2+} handling, including changes in mechanosensitive RyR function (273) due to impaired regulation (287) or to mitochondrial function due to microtubule rearrangement (405).

Some chronic diseases, attributed primarily to cardiac electrical dysfunction, may also include underappreciated beat-by-beat mechanical contributions. An example is long QT syndrome, in which spatially heterogeneous prolongation of repolarization results in increased dispersion of APD, QT prolongation, and a propensity for developing polymorphic ventricular tachyarrhythmias that may give rise to sudden cardiac death (522). Both in transgenic and pharmacological models of long QT syndrome, there is a spatial correlation between regional APD changes and diastolic dysfunction (443), also seen in patients (66), whose extent correlates with individual arrhythmic risk (336). In fact, diagnosis of long QT syndrome may be more straightforward and accurate using spatially resolved deformation imaging (e.g., by MRI) than the more global read-outs provided by ECG. This regional mechanical heterogeneity may contribute to disturbed electrical activity (309). One possible scenario, observed in whole animal models of pharmacologically induced long QT syndrome, are after-contractions in the ventricular subendocardium which stretch (17) and depolarize subepicardial tissue regions, causing afterdepolarizations that may give rise to torsades de pointes (188, 601).

6. Atrial fibrillation

While severe ventricular arrhythmias are lethal, an increasing proportion of our "aging population" lives with AF. Many factors contribute to the initiation and progression of AF, including atrial dilatation, with left atrial enlargement being an independent risk factor for the development of the disease (483, 629, 630). Atrial overload can be acute (e.g., acute pulmonary embolus, myocardial ischemia), transient (e.g., pregnancy), or chronic (e.g., mitral valve disease, hypertension, or changes secondary to HF) (630). Experimental studies of AF have confirmed that acute atrial dilatation increases AF inducibility and sustenance **(FIGURE 9)** (55, 56, 107, 166, 167, 179, 184, 351, 399, 434–436, 506, 621, 672, 673, 691), while an acute reduction of atrial dilatation reduces the vulnerability to AF (263). The increase in AF vulnerability upon acute atrial dilatation is thought to occur due to stretch-induced AP shortening and altered refractoriness (285, 507, 555). Other pro-arrhythmic effects of atrial tissue distension include decreased conduction velocity (107, 562) and altered APD, refractoriness, and conduction, effects that vary locally, in part as a result of

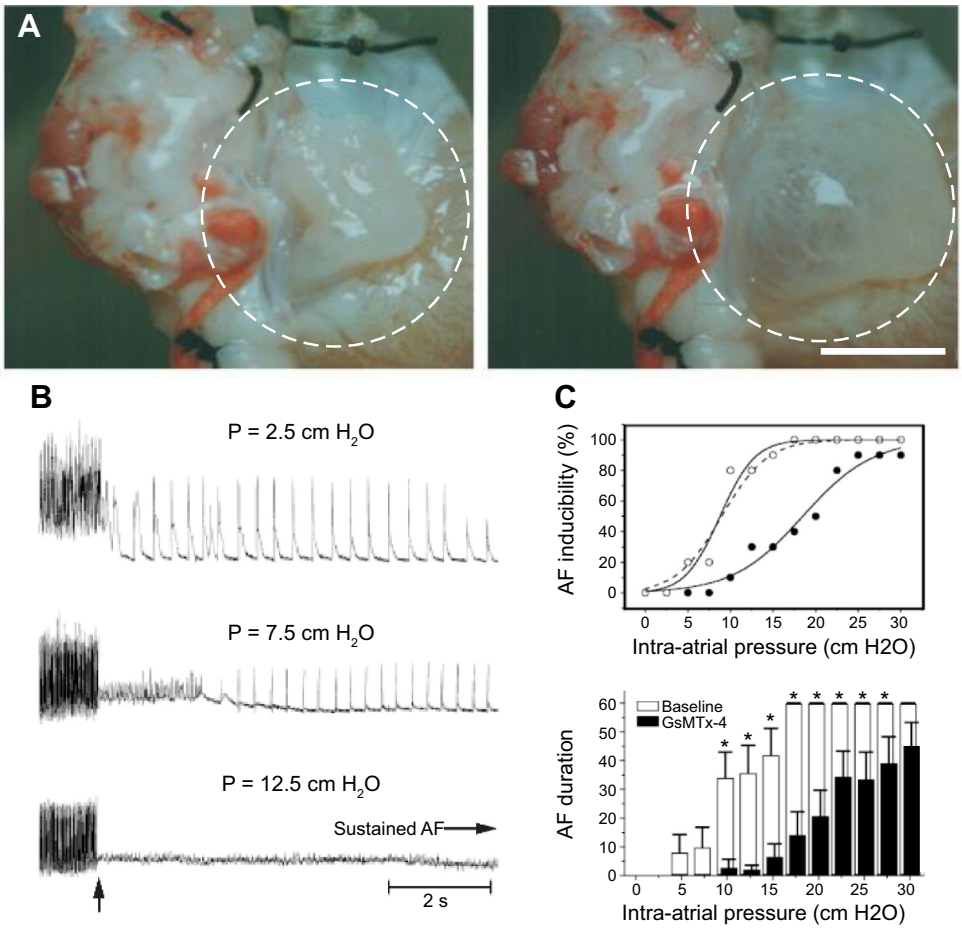


FIGURE 9. Acute stretch increases atrial fibrillation (AF) inducibility. *A*: photographs of the right atrium of a rabbit isolated heart during acute atrial stretch caused by raising intra-atrial pressures from 0 (*left*) to 10 cmH_2O (*right*; scale bar = 1 cm; expanding atria highlighted by dashed circle). [Adapted from Ravelli (506), with permission from Elsevier.] *B*: bipolar atrial electrograms showing an increase in AF inducibility (triggered by bursts of high-frequency pacing, end of burst-pacing indicated by arrow) with increasing intra-atrial pressure. *C*: effect of application of the cation-nonselective stretch-activated channel blocker *Grammostola spatulata* mechanotoxin-4 (GsMtx-4; 170 nM) on AF inducibility (*top panel*: open circles = control, solid circles = GsMtx-4, dashed line = washout) and AF duration (*bottom panel*) as a function of intra-atrial pressure (*$P < 0.05$ vs. baseline). [Adapted from Bode et al. (56), with permission from Springer Nature.]

highly heterogeneous atrial wall thickness (20, 167, 246, 540). Consequently, regions of altered re-entrant cycle length (679) and conduction block (167) can be observed. AF inducibility is also increased upon removal of the pericardium, adding weight to the suggestion that electrophysiological effects of acute atrial dilatation depend on stretch, rather than tissue stress (435).

Some of the above experimental findings have been confirmed in humans. Increased atrial pressure promotes the induction of AF (12), while atrial stretch modulates re-entrant cycle length (508, 649). In patients undergoing cardiac surgery, rapid atrial dilatation decreases conduction velocity and causes signal fractionation (640), while atrial loading modified by atrioventricular pacing decreases the refractory period, conduction velocity, and increases the vulnerability to AF (85, 509, 618). In keeping with these reports, relief of chronic atrial stretch after percutaneous mitral balloon commissurotomy results in an increase in refractoriness and a decrease in its heterogeneity (564).

7. Summary

Depending on magnitude and timing, as well as on the underlying electrical and mechanical background, global and local mechanical stimulation can generate excitation and a substrate for re-entry (resulting in sustained arrhythmias during a narrow and regionally varying vulnerable window for mechanically induced tachyarrhythmias), or lower the threshold for electrically-induced arrhythmias, both in experimental models and humans. This occurs, for example, in the settings of commotio cordis, acute regional ischemia, mitral valve prolapse, and AF. In chronic diseases associated with mechanical changes, such as an increase in preload (end-diastolic volume overload) or afterload (increased arterial blood pressure or outflow resistance), there may also be a contribution of MEC to arrhythmogenesis that is additional to the existing pro-arrhythmic substrate, as evidenced by temporary changes in arrhythmia incidence with acute changes in load. Determining direct causal effects of MEC on cardiac rhythm is challenging and requires further experimental and computational consideration.

D. Arrhythmia Termination

1. Tachyarrhythmias

The anti-arrhythmic potential of cardiac mechanical stimulation had been first noted anecdotally as far back as the 1930s. Mechanical interaction of needles with the myocardium in the context of the then so-called "intra-cardiac therapy" (for adrenalin injections to "revive the dead") were shown to have the potential of restarting the asystolic heart even in the absence of drug injections (250). Later on, targeted myocardial contact of intracardiac catheters has been used to terminate atrial, junctional, and ventricular tachycardia (35, 57, 94, 381, 444, 466, 669), as well as AF (338). Several reports have also found a link between an abrupt increase in intrathoracic pressure, due to coughing (135) or during the Valsalva maneuver (648), and termination of ventricular tachyarrhythmias.

The potential for extracorporeal mechanical stimulation for termination of tachyarrhythmias, on the other hand, received little attention until the 1970s, when a paper detailing the use of precordial thump (a single forceful blow to the lower half of the sternum using the lateral aspect of a closed fist) to defibrillate the tachycardic heart was published (470). It has been shown since that precordial thump may be used in some settings to terminate a host of ventricular tachyarrhythmias, as communicated in case reports and uncontrolled studies [summarized in Ref. 469, with additional reports since (266, 560, 624, 656)].

Few prospective studies of precordial thump have been published, all of which demonstrated extremely low success for termination of ventricular tachyarrhythmia (below 2%; Refs. 11, 82, 216, 467). In contrast, precordial thump applied to the heart in primary asystole may make relevant contributions to restoration of spontaneous circulation in patients (467) (as discussed in sect. II*D2*). It is important to note that the clinical utility of precordial thump in emergency settings is a function of time-since-collapse, as all reported successful cases of precordial thump-induced cardioversion occurred early during the development of ventricular tachycardia or in early VF (21, 35). Animal models of precordial thump have shown a matching disparity of results, with success rates ranging from 0% in an asphyxiated dog model of VF (equivalent to very late application; Ref. 675) to 95% in a post-infarction pig model (198), suggesting that the utility of precordial thump may be inversely related to myocardial tissue energy availability.

Computational modeling has helped in understanding probable mechanisms of successful precordial thump. In these models, successful precordial thump interrupts tachyarrhythmias by stretch-induced excitation of cells in the excitable gap(s), which obliterates re-entrant activity and results in return to sinus rhythm if no re-entrant waves survive or are created (310) (discussed further in sect. IV*B3*). However, when the heart is severely ischemic, as will often be the case in out-of-hospital VF, the mechanical augmentation of metabolically preactivated ATP-sensitive K^+ current ($I_{K,ATP}$) can account for the reduced efficacy of precordial thump (310) (discussed further in sect. IV*B2*).

2. Bradycardia and asystole

One of the first reports in the Western medical literature of the anti-arrhythmic effects of precordial mechanical stimu-

lation was published in 1920, when Eduard Schott demonstrated that rhythmic fist thumps, applied to the precordium (now commonly referred to as "precordial percussion," "percussion pacing," or "fist pacing"), each triggered competent ventricular contractions, which maintained patient consciousness during acute Stokes-Adams attacks (disturbances in atrioventricular conduction that decrease cardiac output and can give rise to loss of consciousness and death; Ref. 545). Unlike the utility of precordial thump for termination of ventricular tachyarrhythmias, which has been generally disappointing, triggering contractions in the bradycardic or asystolic heart seems to work more reliably so that the use of precordial percussion pacing to treat asystole in the emergency setting has been a well-received concept (396, 541, 661).

In a number of case reports (3, 41, 134, 156, 157, 164, 165, 199, 200, 396, 411, 445, 537, 619), percussion pacing has been shown to be relatively effective in triggering electrical activation and competent contractions in the bradycardic or asystolic heart. In the few case series of precordial percussion pacing reported in the literature, a total of 139 patients have been mechanically paced, with a 93% success rate (306, 692, 701). Similarly, finger-tapping of the heart is generally an effective means for cardiac surgeons to restore rhythmic contractile activity while weaning the heart from cardiopulmonary bypass, especially when electrical defibrillation attempts have put the heart into asystole.

Experimental studies of the asystolic post-electrical defibrillation shock period (377) or of cardiac standstill due to complete atrioventricular block (637) have also demonstrated that percussion pacing is a relatively effective means of mechanically stimulating heart beats **(FIGURE 10)**. It has also been shown that passive chest compressions, applied for cardiopulmonary resuscitation, can lead to ventricular excitation, resulting in active cardiac contractions (451, 452). However, since its inception, interest in percussion pacing has always been contrasted by questions about its utility (675, 702), fueled by a lack of prospective clinical studies (469) and mechanistic explanations.

Overall, it appears that single or serial precordial thumps (often called precordial percussion) may have some utility in the asystolic or severely bradycardic heart. Importantly, ventricular contractions resulting from mechanically-induced excitation (which triggers active contraction) are hemodynamically more productive than external chest compressions (which generate circulation by passive ventricular ejection): cardiac output is 77% of baseline for mechanically-induced excitation, compared with 38% of baseline even with optimally performed chest compressions (98, 262). Thus percussion pacing could have some utility in maintaining adequate circulation in the asystolic heart in emergency setting.

Based on the potential of precordial mechanical stimulation as a rapid and noninvasive means of cardiac pacing, several

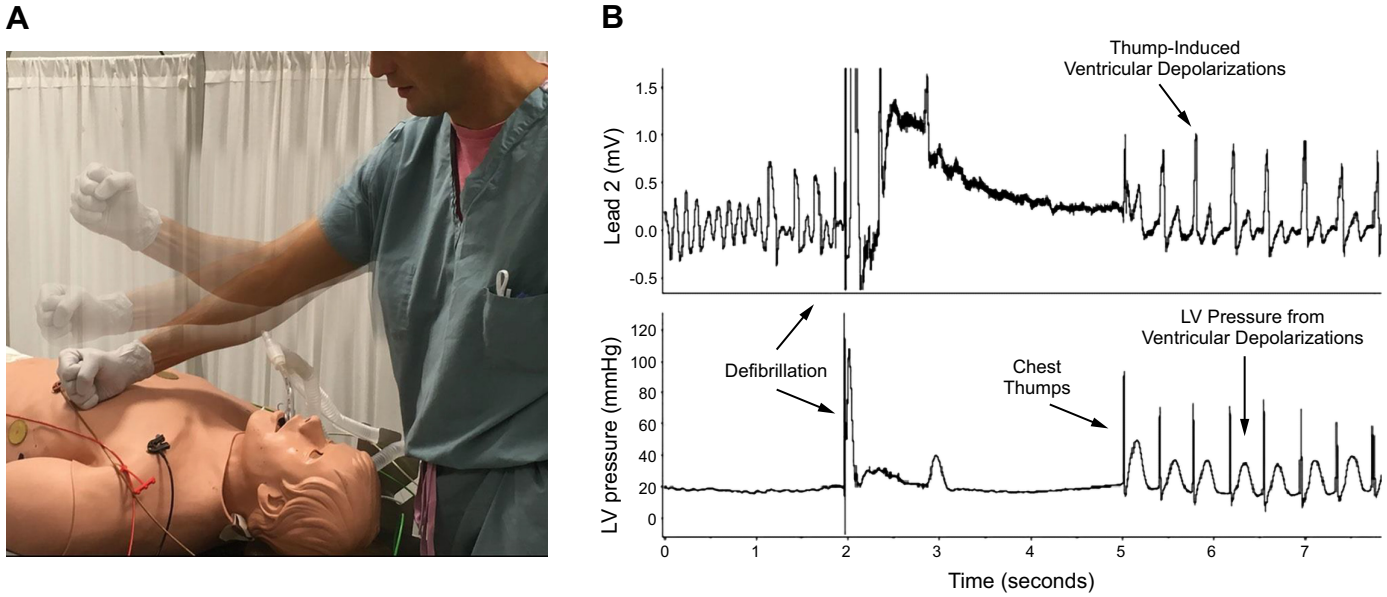


FIGURE 10. Precordial fist thumps for mechanical pacing. *A*: technique of percussion pacing, using short sharp blows with the ulnar side of the clenched fist from a height of ~30 cm to the lower left sternal edge. [From Giordano et al. (200), with permission from Wolters Kluwer Health.] *B*: termination of ventricular fibrillation by external defibrillator shock in an anesthetized pig, followed by a single ventricular contraction and 2 s of asystole. A series of chest thumps then results in active ventricular depolarization (electrocardiogram lead 2; *top row*) and left ventricular (LV) contractions (LV pressure; *bottom row*). [From Madias et al. (377), with permission from Elsevier.]

techniques for applying mechanical stimuli to the heart have been developed (488). In 1976, pacemaker, defibrillator, and resuscitation pioneer Paul Zoll developed a device for temporary mechanical pacing (the "Cardiac Thumper") (700), which was effective in evoking repetitive heartbeats in patients with asystole after VF, with AF, or with atrioventricular block, as well as in dogs with normal sinus rhythm or atrioventricular block (701) **(FIGURE 11)**. Other mechanical stimulation devices have been devised, including patents for an extracorporeal mechanical pacer that stimulates the heart via pressure waves applied to the precordium (228), and an implantable mechanical defibrillator that applies a mechanical shock to the heart by a piezotransducer generated pressure wave transmitted through a hydraulic line to a balloon-head in contact with the myocardium (233).

While precordial percussion is an immediately accessible form of extracorporeal pacing that is potentially well-suited for out-of-hospital emergency settings, more recent device-based efforts have focused on the use of extracorporeal high-intensity focused ultrasound (319) as a potentially more controlled means of externally applying mechanical stimuli to specific regions of the myocardium, over longer periods. The bioeffects of ultrasound have been extensively studied (motivated by the assessment of its safety for use in echocardiography) and are dependent on tissue properties (e.g., density, attenuation, absorption), exposure (e.g., frequency, intensity, pulse duration/duty cycle), and beam configuration (137). Ultrasound-induced tissue deformation can occur as a result of acoustic radiation force (a consequence of momentum transfer from the ultrasound wave to the tissue) which can lead to excitation of the heart, one of the known side effects of high-intensity focused ultrasound lithotripsy (121, 138, 149, 162, 207, 286, 665, 667). The first report of the excitatory effects of ultrasound on the heart came from E. Newton Harvey in 1929, who noted that in frog and turtle hearts high-frequency ultrasound caused an increase in HR or the resumption of regular beating of an otherwise quiescent ventricle (226). Subsequent studies have shown similar ultrasound-induced excitation in frog (139), mouse (376), and rat (229) hearts, as well as cultured neonatal ventricular cardiomyocytes (177), which, as for direct mechanical stimulation, appears to be driven by activation of SAC (324). Short periods of mechanical pacing by repetitive high-intensity focused ultrasound have also been used for excitation in pigs with hypoxia-induced bradycardia (613), in anesthetized rats (368), and in ex vivo and in vivo pig hearts, occasionally using intraventricular contrast agents to enhance energy transfer (387) **(FIGURE 12*A*)**.

Beyond precordial percussion and high-intensity focused ultrasound, there have been reports of the use of time-varying magnetic fields to excite the heart, which by-and-large has proven to be impractical due to high-energy requirements and unreliable pacing capture (63, 260, 418, 653, 676–678). These have inspired an alternative approach for the delivery of cardiac mechanical stimulation using electromagnet-manipulated intravenously-injected magnetic microparticles (528). Using an electromagnet to localize intravenously-injected magnetic microparticles in the ventricles, and then periodically forcing them against the myocardium using an alternating magnetic field, allowed mechanical pacing in ex vivo and in vivo rat hearts, as well as in vivo in pigs **(FIGURE 12*B*)**.

3. Advantages and limitations of MEC-based antiarrhythmic interventions

The above discussion highlights the potential utility of mechanical pacing for the asystolic or severely bradycardic heart. Perhaps most importantly for its use, by triggering active contractions, mechanical pacing generates a greater stroke volume than external chest compressions that passively squeeze blood from the cardiac chambers (98, 262). On top of this, extracorporeal mechanical pacing is more targeted, has low energy requirements [0.04–1.5 J (701), compared with 150 J or more that are used for electrical defibrillation (572)], and it is less painful than transthoracic (transcutaneous) electric stimulation (the alternative available method for temporary extracorporeal pacing), so it has some advantages that ideally one would wish to garner in the clinical setting. For instance, due to nerve and skeletal muscle activation causing painful spasms, transthoracic electric stimulation typically necessitates the use of a seda-

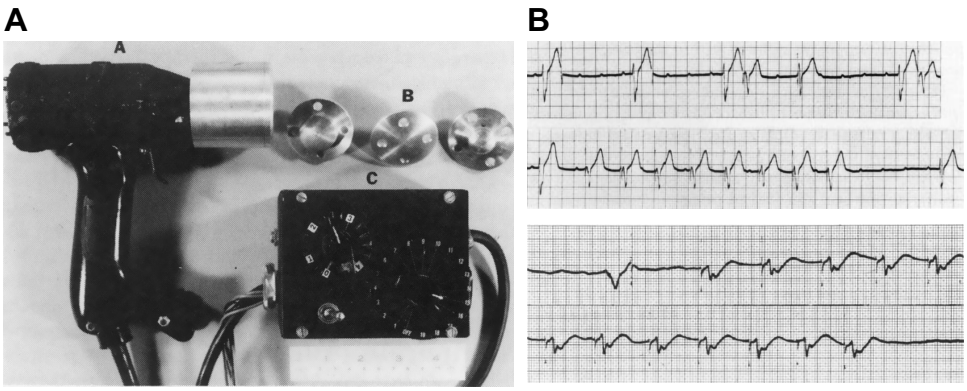


FIGURE 11. "Cardiac thumper" device for temporary mechanical pacing. *A*: mechanic pacing device (fashioned from a modified electrically powered stapling gun). *B*: electrocardiogram of an anesthetized dog in complete heart block (*top*) and a patient in cardiac arrest (*bottom*) being mechanically paced by the external mechanical pacemaker (mechanical stimuli marked by spike-like artifacts). [From Zoll et al. (701), with permission from Massachusetts Medical Society.]

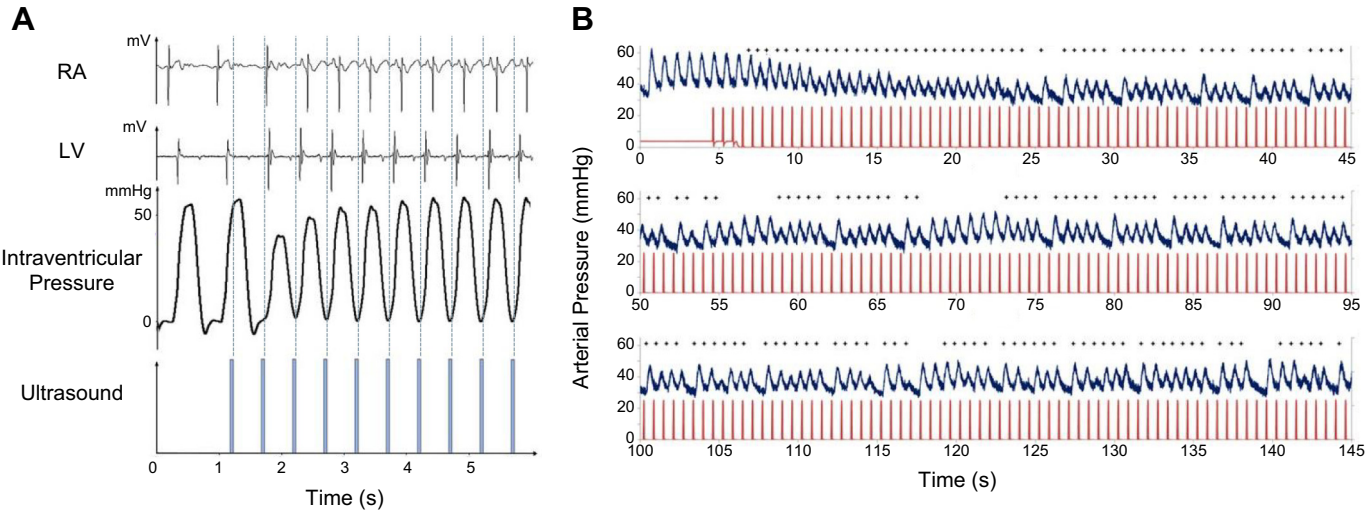


FIGURE 12. Mechanical pacing. *A*: electrocardiogram from right atrium (RA) and left ventricle (LV) and hemodynamic recordings (LV pressure) of ultrasonic LV pacing in a pig isolated heart, showing that upon ultrasound application LV excitation and pressure development precede atrial excitation. [Adapted from Marquet et al. (387).] *B*: arterial pressure (blue line) and the current through an electromagnet coil (red line) during mechanical pacing using electromagnet-manipulated intravenously injected magnetic microparticles in an anesthetized pig (+ signs indicate pacing capture). [From Rotenberg et al. (528).]

tive or aesthetic agent, which may further impair the critical hemodynamic condition of a patient (416).

However, mechanical pacing is not without its own limitations. High-intensity focused ultrasound has been shown to cause cell and tissue damage (352, 353, 400–402, 690), and direct mechanical stimulation may give rise to contusional effects (117, 492, 494), so stimulation energy levels must be carefully considered and well controlled [not usually possible with manual application, though the maximum energy most physicians will be able to apply by fist thumps from the recommended 30 cm height is below 10 J (468)]. Another major concern for cardiac mechanical stimulation is the potential for the induction of sustained arrhythmias (discussed in sect. IIC). Precordial thump, for instance, has been shown to carry a risk of causing rhythm deterioration (425, 559) and, while rare, ventricular tachyarrhythmias have been reported to occur with precordial percussion (306), high-intensity focused ultrasound (when used with an intraventricular contrast agent) (387), and even with chest compressions (451, 452). Thus, in applications of mechanical pacing, timing relative to any underlying rhythm should be considered, as is common for cardiac electrical stimulation. For mechanical pacing with magnetic microparticles, there are additional concerns relating to particle biocompatibility and their excretion, as well as potential coronary block and vascular embolism (528).

Another important consideration for the utility of mechanical pacing is the loss of capture that has been observed in many studies upon repeat application of mechanical stimuli. High-intensity focused ultrasound-based mechanical pacing in anesthetized rats, for example, was effective for a maximum of seven consecutive stimuli, despite low pacing rates (once per breathing cycle; Ref. 368). Mechanical pacing in the presence of magnetic microparticles in the heart was marginally more successful, with ~30 stimulated beats in anesthetized rats and pigs before loss of 1:1 capture occurred (528) **(FIGURE 12*B*)**. Even though fist-pacing has been reported to be possible over longer periods in severely bradycardic patients (described in sect. IV*D2*), the published case reports generally did not monitor whether 1:1 capture was indeed sustained, and in many cases, treatment was interspersed with periods of spontaneous circulation, so the sustainability of mechanical pacing in human is currently unknown.

The apparent lack of sustainability of mechanical pacing in the above studies was attributed to a loss of magnetic microparticles (528) or contrast agent (when used to enhance the effects of high-intensity focused ultrasound-based stimulation) (387) at the pacing site, or to disruption of myocyte homeostasis (such as a mechanically-induced increase in intracellular Ca^{2+} levels) (368). Studies of mechanical pacing by gentle mechanical contact with the epicardium of ex vivo hearts have corroborated a loss of capture (494, 696) and demonstrated that this effect is pacing rate dependent, suggesting that loss of mechanical stimulation efficacy may be a fundamental biological limitation of mechanical stimulation itself (494) **(FIGURE 13)**. While the mechanisms for the loss of capture with repetitive mechanical stimulation have not yet been identified, loss of capture appears to relate to an MEC adaptation period during which mechanical, but not electrical, excitability is reduced. As capture with mechanical stimulation is restored after a period of normal sinus rhythm, it appears that mechanical and electrical stimulation are limited by different types of "refrac-

toriness." This concept is supported by *1*) ex vivo studies of intraventricular balloon inflation (151) and stimulation of myocyte monolayers by fluid jets (320), in which repeat stimulations were effective only after periods of rest up to 1 min for full recovery of mechanically-induced excitability; and *2*) in vivo studies of repetitive local ventricular stimulation that demonstrated a decrease in the effective refractory period with electrical but not mechanical stimulation (18).

There are several potential mechanisms that could account for mechanical refractoriness that is distinct from electrical refractoriness, including effects of mechanical stimulation on tissue mechanical properties, ion distributions in cardiac cells, or SAC and stretch-modulated ion channel activity.

Mechanical stimulation is known to affect myocardial mechanics. Repeated axial stretch of ventricular myocardium (by 5–15%) has been reported to cause a small decrease in muscle stiffness, which recovers after ~30 s of rest (302). This viscoelastic effect could contribute to formation of an MEC adaptation period, especially considering that loss of capture with mechanical pacing is accelerated as stimulation frequency is increased. On the other hand, a possible role for changes in cellular ion balance(s) in the loss of mechanical pacing capture, specifically via mechanical modulation of Ca^{2+} handling (81), could be based on an acute stretch-induced increase in localized SR Ca^{2+}-release events ("Ca^{2+} sparks"), which may reduce SR Ca^{2+} levels (190, 257, 258, 474, 481, 482), or on Ca^{2+} release from mitochondria, whose intraorganelle Ca^{2+} concentrations may also be affected (36, 37, 405, 412). If Ca^{2+} is involved in mechanically-induced excitation, then a depletion of mechanically releasable subpools of Ca^{2+} could affect the efficacy of mechanical stimulation. Stretch-induced Ca^{2+} release from the SR may result either from direct mechanical stimulation of RyR (258) or arise via effects mediated by mechanically-stimulated reactive oxygen species (ROS) production (481). Both mechanisms could be affected by the frequency of cyclic mechanical stimulation, which could help to explain the decrease in the number of mechanical stimulations before a loss of pacing capture when stimulation rate is increased (494).

Perhaps the most convincing potential mechanism contributing to pacing loss, however, is the fact that SAC_{NS} themselves show "mechanical refractoriness" in the heart (i.e., the first response to stretch is larger than subsequent ones). This is supported by the observation in cardiac cells that repeated mechanical stimulation causes a cumulative reduction in $I_{SAC,NS}$ due to channel inactivation, unless stimulations are spaced minutes apart (48, 49, 242). At the whole heart level, this reduction in $I_{SAC,NS}$ results in a continuously increasing delay between mechanical stimulation and excitation with successive stimuli (696). Although it has not been studied in cardiac myocytes, mechanically-induced current through Piezo channels has been shown to decrease with repetitive stimulation (e.g., in HEK293t cells expressing the ion channel). In sensory dorsal root ganglion neurons, this leads to a stimulation frequency-dependent loss of mechanically-induced excitation (349), as seen with mechanical pacing in the heart. SAC "desensitization" or "rundown" is in fact a broadly reported phenomenon and a common observation in patch-clamp studies. It has been observed, for instance, in the two-pore K^+ domains in a

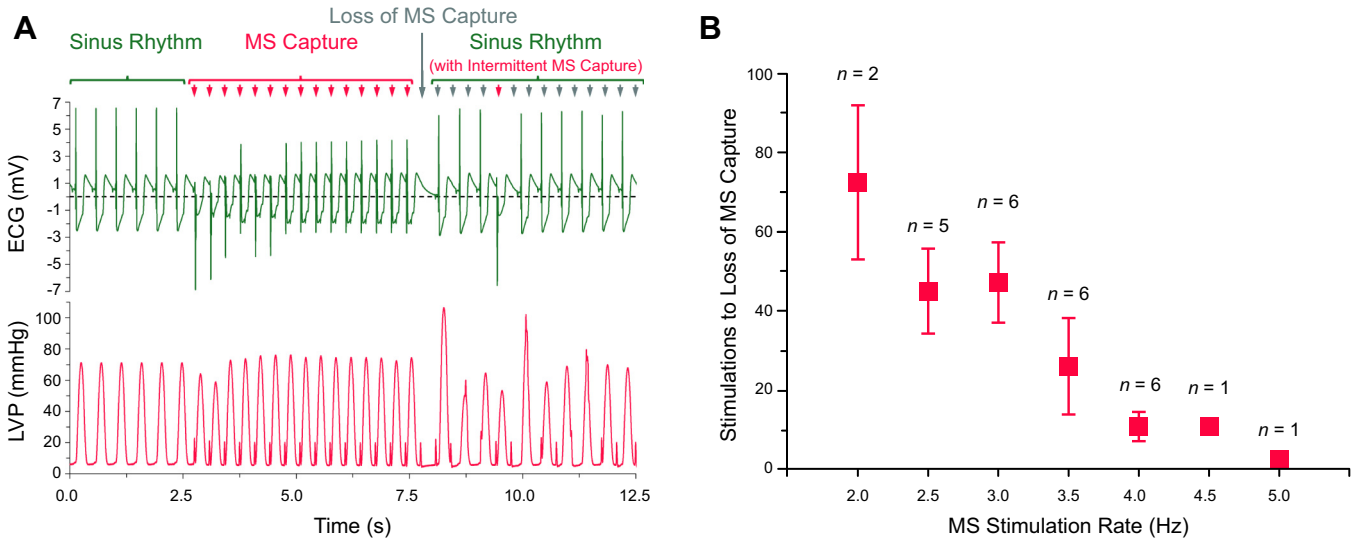


FIGURE 13. Loss of mechanical pacing capture. *A*: electrocardiogram (ECG, *top curve*) and left ventricular pressure (LVP, *bottom curve*) recorded from an isolated Langendorff-perfused rabbit heart during sinus rhythm, followed by a train of focal left ventricular mechanical stimulations (MS; see short pressure spikes preceding mechanically induced contractions, *bottom curve*), with a transient period of 1:1 capture, followed by return to sinus rhythm with intermittent MS beats. *B*: effect of varying rate of MS on the number of stimulations to loss of 1:1 capture. [Adapted from Quinn and Kohl (494).]

weak inwardly rectifying K^+ (TWIK)-related K^+ channel-1 (TREK-1) (237). A similar use-dependent decrease in SAC could be responsible for the inverse dependence of the number of mechanical stimulations to a loss of pacing capture on the mechanical stimulation rate.

Even though it appears that 1:1 capture may not be maintainable for extended periods of repetitive mechanical stimulation at physiological rates, it is possible that mechanical pacing is effective at rates below normal sinus rhythm, accounting for clinical case reports on its utility in patients with bradycardic or asystolic hearts, who have been kept conscious during prolonged ventricular asystole for periods of close to 3 h (3).

4. Summary

Precordial mechanical stimulation, whether by precordial impact, high-intensity focused ultrasound, or other device-based means, can cause excitation of the heart and may hold important therapeutic potential for temporary pacing or, less compellingly, tachyarrhythmia termination in emergency settings. Mechanical rhythm management is not without limitations, however, including lack of sustainability, safety, and ethical (hitting a patient) concerns. Based on the *2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations* (440), current International Liaison Committee on Resuscitation (ILCOR) (321, 582) and American Heart Association (74, 362) guidelines state that "precordial thump may be considered for patients with witnessed, monitored, unstable ventricular tachyarrhythmias, including pulseless ventricular tachycardia if a defibrillator is not immediately ready for use" (74), but "should not be used for unwitnessed out-of-hospital cardiac arrest" (74). The need for further research into the utility of mechanical heart rhythm management in severe bradycardia is highlighted as follows: "there is insufficient evidence to recommend for or against the use of the precordial thump for witnessed onset of asystole caused by atrioventricular conduction disturbance" (321). Regarding percussion pacing, the guidelines state that "fist pacing may be considered in hemodynamically unstable bradyarrhythmias until an electric pacemaker (transcutaneous or transvenous) is available" (582), but that "there is insufficient evidence to recommend percussion pacing during typical attempted resuscitation from cardiac arrest" (96). These recommendations reflect a paucity of prospective data and a general lack of understanding of the efficacy, limitations, and mechanisms of mechanical rhythm management, justifying future study of its optimization and potential clinical utility in particular in asystole and severe bradycardia, the rhythm disturbance for which precordial thump was originally reported.

E. Knowledge Gaps and Future Directions

- The critical characteristics of mechanical stimulation, such as timing, force versus deformation, application rate, and site of application, are largely unexplored, deserving further research.
- The mechanisms and importance of SAN mechano-sensitivity for maintaining normal sinus rhythm, and mechanical contributions to SAN dysfunction with age and disease, are unknown; this and the interplay of V_m, Ca^{2+}, and mechanics oscillators in sustaining SAN activity and autoregulation warrant further investigation in experimental models and human studies.
- For ventricular mechanical stimulation, observed responses include a wide variety of electrophysiological changes, but the source of this variability is unclear; aspects relating to differences in species, mechanical stimulation characteristics, or underlying physiology need to be explored.
- The potential role of non-myocytes (such as fibroblasts, macrophages, or intracardiac neurons) in MEC responses is just emerging, and much remains to be explored; the use of innovative targeted technologies, such as optogenetics, holds promise for addressing this new frontier.
- While hallmark examples of the arrhythmogenic and anti-arrhythmic potential of MEC in acute settings have driven conceptual and computational model development to link molecular and clinical observations, mechanistic insight into MEC-mediated behavior in chronic diseases, their mechanisms of action, and potential for therapeutic exploitation, have not been established; this is a critical area for targeted investigation.
- MEC contributions to anti-arrhythmic interventions seem most relevant in the asystolic or severely bradycardic heart. The source of the observed loss of mechanical trigger efficacy with repetitive stimulation is unknown; further investigations are essential for the clinical translation of mechanically-based pacing.

III. MOLECULAR MECHANISMS OF MEC

A. Pacemaker Cells

1. Mechano-sensitivity of "mechanical oscillator" components

In the microelectrode recording experiments of Klaus Deck **(FIGURE 14*A*)**, the increase of spontaneous diastolic depolarization and beating rate during SAN stretch were accompanied by a decrease in the absolute values of both maximum diastolic and maximum systolic potentials (147). In other experiments, the need for a minimum mechanical pre-

load to establish rhythmic SAN excitation also involved a progressive reduction in the absolute value of the maximum diastolic potential with stretch, which resulted initially in the appearance of subthreshold oscillations of V_m, followed by spontaneous beating (337) **(FIGURE 3*A*)**. Isolated Purkinje fibers also respond to stretch with diastolic depolarization, which, once it exceeds a certain level, gives rise to arrhythmic AP generation, followed by loss of excitation (292).

These findings helped in narrowing the range of plausible molecular mechanisms involved in the chronotropic response to stretch, as any components affecting V_m would be expected to have their reversal potential (E_{rev}) somewhere between maximum diastolic and systolic potentials. Initial targeted electrophysiology studies used positive pressure inflation (via the patch pipette in a whole-cell model) of rabbit isolated SAN cells, which stimulated the swelling-activated chloride current ($I_{Cl,swell}$) (213), as well as $I_{Ca,L}$ (389). With an E_{rev} near 0 mV in cardiac myocytes, $I_{Cl,swell}$ could theoretically account for the observed stretch-induced changes in SAN electrophysiology. However, there is a time-lag between the onset of cell swelling and activation of $I_{Cl,swell}$ (usually exceeding 1 min), rendering it too slow for the near-instantaneous changes upon acute stretch. Additional studies using hypo-osmotic swelling of spontaneously beating rabbit SAN cells in perforated patch mode demonstrated a swelling-induced reduction, rather than the expected increase, in beating rate (343). These experiments were accompanied by computational simulations, suggesting that the decrease in beating rate is caused by cytosol dilution (343). It was shown that this effect, via a decrease in intracellular K^+ concentration, could have reduced the rapid delayed rectifier K^+ current, shifting the maximum

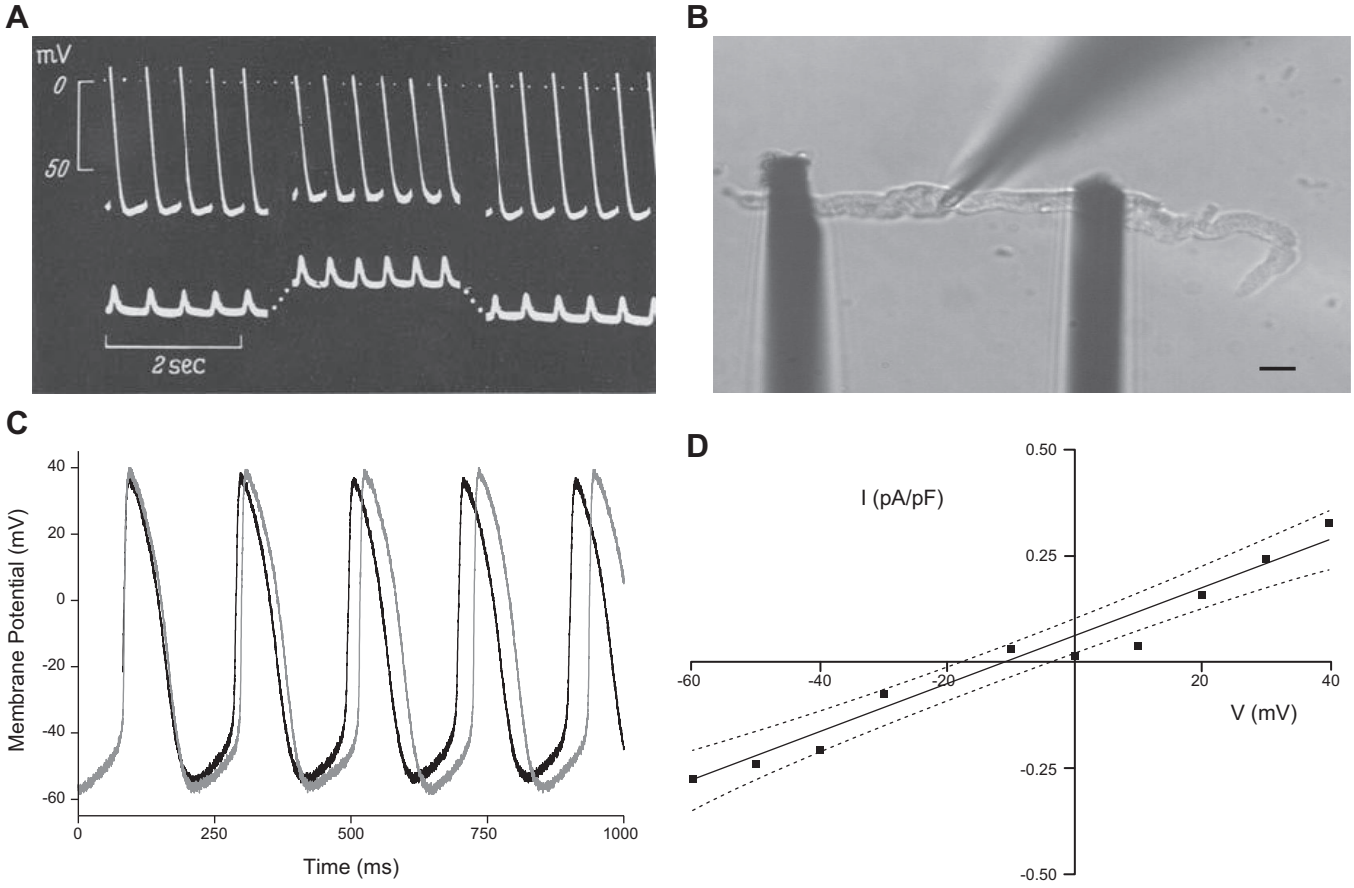


FIGURE 14. Stretch-induced increase in sinoatrial node beating rate. *A*: intracellular sharp electrode recordings of transmembrane potential (*top*) and applied and generated force (*bottom*; passive stretch and active contraction pointing upwards) in cat isolated sinoatrial node tissue, showing an increase in beating rate during stretch, combined with a reduction in absolute values of maximum diastolic and maximum systolic potentials. [From Deck (147).] *B*: axial stretch, applied to a spontaneously beating rabbit sinoatrial node cell using a pair of carbon fibers (scale bar = 10 mm). *C*: patch-clamp recordings of transmembrane potential showing a stretch-induced increase in spontaneous beating rate of the pacemaker cell, accompanied by a reduction in the absolute values of maximum diastolic and maximum systolic potential (light curve = before stretch, dark curve = during stretch). [From Cooper et al. (120).] *D*: whole-cell stretch-induced current (*I*)-voltage (*V*) relation (*I* is the difference current in absence vs. presence of streptomycin to block cation-nonselective stretch-activated channels, normalized to cell capacitance) from rabbit isolated sinoatrial node cells, showing a reversal potential of about −11 mV (dotted lines = 95% confidence limits). [From Cooper et al. (120).]

diastolic potential towards more depolarized levels and reducing I_f, as confirmed experimentally in voltage-clamped SAN cells (343).

It should be noted that cell inflation, whether by positive pressure inflation or swelling, is mechanically different from axial stretch, as swelling is associated with an increase in cell diameter and negligible changes in length. In contrast, axial stretch causes cell lengthening, a reduction in diameter (as cell volume is understood to remain constant during acute length changes), and an increase in beating rate of spontaneously beating rabbit SAN cells (120). Even in isolated cells, this is accompanied by a reduction in the absolute values of maximum diastolic and maximum systolic potential, as seen in SAN tissue **(FIGURE 14, *B* AND *C*)**.

Subsequent V_m-clamp studies revealed that stretch of single SAN cells indeed gives rise to a stretch-activated current with an E_{rev} near −11 mV (120) **(FIGURE 14*D*)**. This current is compatible with SAC_{NS} (133, 209) **(FIGURE 15)**, whose block indeed causes a reduction of the chronotropic response to SAN stretch (119).

Interestingly, while in larger mammals with inherently slow background HR, the chronotropic response to SAN stretch is "positive" (increase in beating rate), in smaller mammals such as mouse and rat with resting HR of 600 beats/min or more, SAN stretch can decrease beating rate (119). Perhaps counterintuitively, both responses may be accounted for by activation of SAC_{NS}. In mammals with slower background HR, the SAN AP is characterized by a relatively slow AP upstroke (carried mainly by $I_{Ca,L}$) and a relatively prominent plateaulike early repolarization phase, while mammals with faster HR exhibit faster upstrokes (often carried by a mix of Na^+ and Ca^{2+} currents; Ref. 344) and swift initial repolarization, giving rise to a more spikelike AP shape. Consequently, "slower" SAN AP spend the majority of each cycle moving their V_m towards the E_{rev} of SAC_{NS}, while "faster" SAN AP spend a larger proportion of time moving their V_m away from it **(FIGURE 16)**. Thus activation of $I_{SAC,NS}$, which "pulls" V_m in the direction of its E_{rev}, would be expected to increase slower and reduce faster beating rates (118), a concept that has been supported quantitatively by computational modeling (120) (discussed in sect. IV*A1*). This concept is also supported by recent experimental data from zebrafish, whose HR (~120 beats/min) is closer to that of mammals larger than mice, and whose SAN AP show a relatively slow upstroke and a prominent plateau: stretch of the zebrafish SAN causes a stretch-amplitude-dependent increase in beating rate (375). The difference in the chronotropic stretch response between mouse and other mammals may also relate in part to species-specific structural and mechanical SAN properties, in particular distinct collagen architecture and acute changes that occur with stretch (373a).

2. Mechano-sensitivity of V_m oscillator components

Quantitative plausibility is no substitute for experimental validation (498), and SAN stretch responses might also result from direct effects on stretch-modulated components of the V_m and/or Ca^{2+} oscillators (summarized in **FIGURE 2*C***). In cell expression systems, mechanical stimulation increases the amplitude (88) and both activation and deactivation

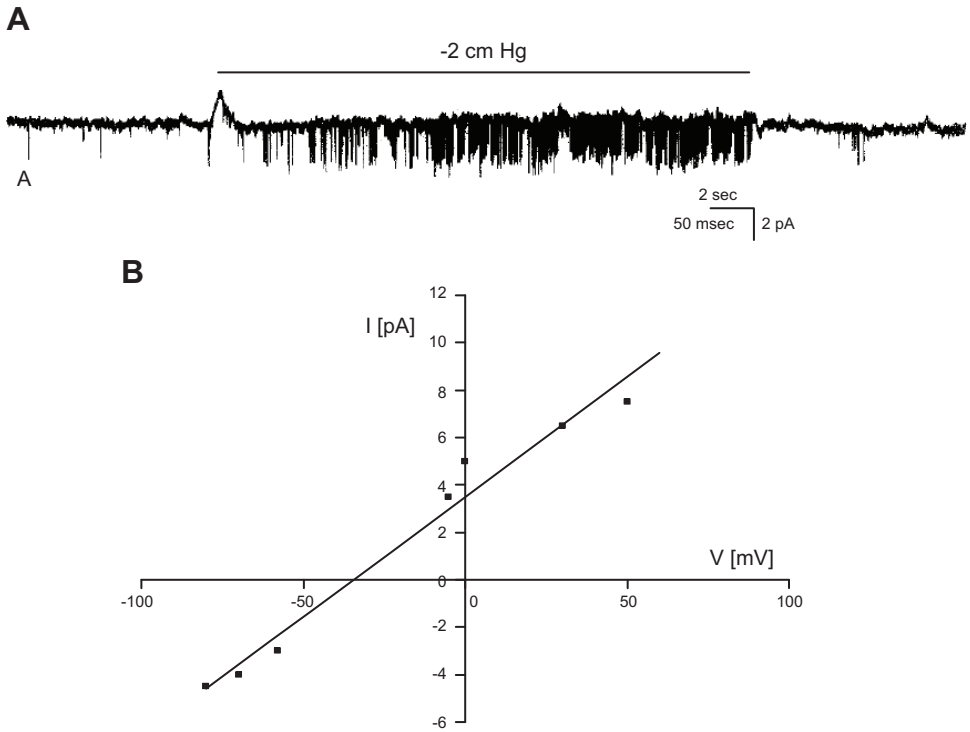


FIGURE 15. Cation-nonselective stretch-activated channel current in cardiac cells. *A*: cell-attached patch-clamp recording of a neonatal rat ventricular myocyte during application of negative pressure (~2 cmHg) to the patch pipette, indicated by the horizontal line, which increases single stretch-activated channel open probability. *B*: current (*I*)-voltage (*V*) relationship of resulting stretch-activated current. [Adapted from Craelius et al. (133), with permission from The Biochemical Society.]

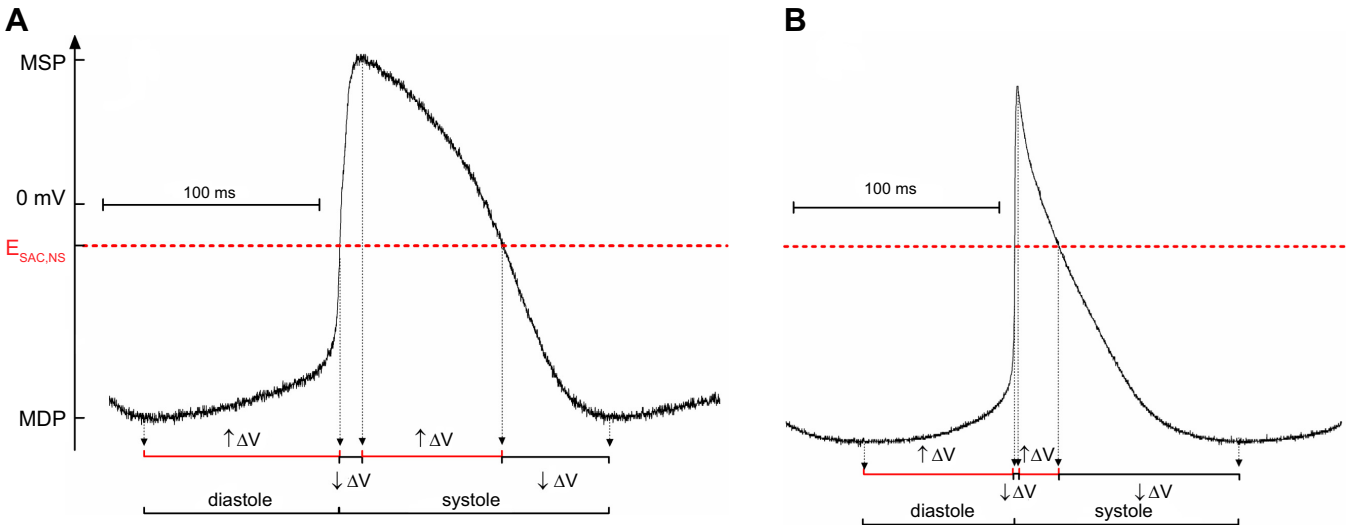


FIGURE 16. Conceptual model of cation-nonselective stretch-activated channel (SAC_{NS}) effects on the action potential (AP) of sinoatrial node (SAN) pacemaker cells of different species. Experimental recordings of transmembrane potential from rabbit (*A*) and mouse (*B*) show the interrelation of key electrophysiological parameters [maximum diastolic (MDP) and maximum systolic (MSP) potential] and the reversal potential of SAC_{NS} ($E_{SAC,NS}$). The time periods during which opening of SAC_{NS} would either accelerate ($\uparrow \Delta V$) or slow ($\downarrow \Delta V$) intrinsic changes in transmembrane potential are indicated at the bottom. In rabbit, SAC_{NS} would accelerate changes during ~70% of the pacemaker cycle, while in mouse this would occur only for ~45% of the time. [From Cooper and Kohl (118), with permission from Elsevier.]

rates (358) of I_f. Interestingly, these effects are dependent on background beating rate: when membrane patches are AP-clamped to cyclic SAN or Purkinje cell AP waveforms, membrane deformation causes an increase in I_f at higher, and a decrease at lower, beating rates, which would be expected to have opposite effects to the observed direction of stretch-induced chronotropic effects. Similarly, $I_{Ca,L}$ but not $I_{Ca,T}$ (77, 373, 594), several K^+ currents (via Kv1, Kv3, Kv7, KvCa) (415), and the Na^+ window current (50) have been shown to be mechanically modulated. This means that their opening probability is sensitive to the mechanical environment, even though stretch per se is not normally sufficient to trigger channel openings on its own. In the beating heart, $I_{Ca,L}$ and the Na^+ window current could be involved in accelerating SAN (390, 409) and Purkinje fiber pacemaking rates (173, 270, 422, 450). In pathological settings associated with myocardial ischemia, $I_{K,ATP}$ may also become important in the mechanical modulation of pacemaker function (51). This current, whose activity, if preactivated by a reduction in ATP levels, is increased by stretch in atrial and ventricular myocytes (627, 628), has been shown to be present in rabbit isolated SAN cells (220). Activation of $I_{K,ATP}$ in the ischemic SAN could be expected to hyperpolarize V_m, opposing spontaneous diastolic depolarization and, potentially at least, the positive chronotropic effect of stretch, yet the ultimate effect on beating rate is unclear, as SAN beating rate is set by competing changes in several current systems whose partially reciprocal dependence on the maximum diastolic potential can stabilize beating rate (such as I_f and $I_{b,Na}$; Ref. 438).

3. Mechano-sensitivity of Ca^{2+} oscillator components

Stretch effects on intracellular Ca^{2+} handling may also modulate SAN beating rate. Stretch has been shown to directly affect intracellular Ca^{2+} handling in cardiac cells (5, 81, 480, 602). In keeping with a contribution of these mechanisms to beating rate regulation, it has been reported that the response to stretch is reduced by interventions that decrease SR Ca^{2+} content by lowering extracellular Ca^{2+} concentration or blocking sarco/endoplasmic reticulum Ca^{2+}-ATPase (14), inhibit SR Ca^{2+} release by RyR block (14), or decrease trans-sarcolemmal Ca^{2+} fluxes, such as upon $I_{Ca,L}$ block (230). As mentioned above (see sect. II*D3*), axial stretch of ventricular myocytes causes an acute increase in Ca^{2+} spark rate (258) **(FIGURE 17)**. In ventricular cells, this may further involve mechanically-induced mitochondrial Ca^{2+} release through mitochondrial I_{NCX} (36, 37, 405, 412). If similar stretch effects on Ca^{2+} handling are present in SAN cells, they could be relevant for mechanical modulation of SAN activity, as changes in SAN intracellular Ca^{2+} concentration (682) or mitochondrial I_{NCX}-mediated changes in Ca^{2+} spark rate (683) may affect beating rate.

In addition, there may be secondary effects of altered Ca^{2+} handling through store-operated Ca^{2+} channel current (an inward Ca^{2+} current whose magnitude depends on the level of depletion of SR Ca^+ stores; Ref. 548). While not generally included as a component of the Ca^{2+} oscillator, this current has been implicated in modulation of SAN beating rate, both directly via a background inward current that is modulated by beat-by-beat changes in SR Ca^{2+} content

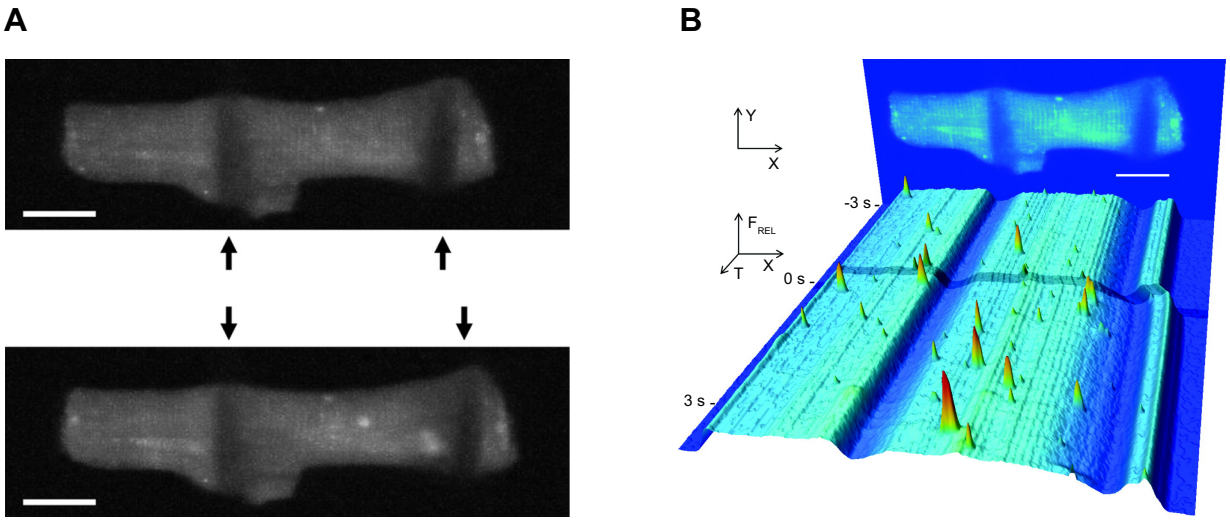


FIGURE 17. Effect of axial stretch on calcium (Ca^{2+}) spark rate in rat ventricular myocytes. *A*: confocal images of intracellular Ca^{2+} concentration showing an acute increase in Ca^{2+} spark activity upon axial stretch (change in sarcomere length of 8% from control) applied by carbon fibers to only one half (right side, see arrow marks) of an isolated cardiomyocyte. *B*: time course of relative intracellular Ca^{2+} concentration signal intensity, illustrating the local nature of the stretch-induced (applied at time point 0 s) increase in Ca^{2+} spark rate in the distended part of the cell only (individual spark dynamics remain unchanged; scale bars = 20 μm). [From Iribe et al. (258), with permission from Wolters Kluwer Health.]

(277), and indirectly through secondary effects via electrogenic I_{NCX} activity (276). Moreover, it has been suggested that the store-operated Ca^{2+} channel may be accounted for by transient receptor potential (TRP) canonical protein (TRPC) expression (277). Since type 1 of TRPC has been suggested to underlie SAC_{NS} (386), it could play a much more important role in direct Ca^{2+}-mediated mechanical effects on cardiac pacemaker activity than hitherto appreciated.

4. Summary

Mechanical activation of SAC_{NS} can explain most aspects of the chronotropic response to SAN stretch. Stretch causes an increase of spontaneous diastolic depolarization and a decrease in the absolute values of maximum diastolic and maximum systolic potentials, due to the E_{rev} of SAC_{NS} being between −20 and 0 mV. As a result, beating rate is increased with stretch in most animals. In species with high HR and fast early repolarization such as mouse, however, beating rate can be decreased with SAN stretch, even though this response may be explained by the same molecular mechanism: SAC_{NS} activity. While SAC_{NS} can explain most aspects of the chronotropic response to SAN stretch, there may be important contributions of mechanical effects on components of the V_m and Ca^{2+} oscillators. Many factors involved have been shown to be subject to mechanical modulation, including various ion currents (I_f, $I_{Ca,L}$, the Na^+ window current, and several K^+ currents) and intracellular Ca^{2+} handling, although most of the related evidence comes from other cardiac cell types or expression systems, so direct confirmation of their involvement in SAN mechano-sensitivity is missing.

B. Working Cardiomyocytes

1. SAC_{NS}

Stretch-induced changes in V_m of working cardiomyocytes can be explained by $I_{SAC,NS}$ **(FIGURE 5*A*)**. Due to an E_{rev} at levels that are around halfway between peak AP and resting V_m, activation of $I_{SAC,NS}$ depolarizes V_m in resting cells (132), causing afterdepolarization-like events in isolated cardiomyocytes (308) and, if suprathreshold, premature excitation (521, 658). During the AP plateau, $I_{SAC,NS}$ accelerates V_m repolarization, causing a shortening of early APD (659, 688). As a result, AP shortening has frequently been observed with sustained stretch (659). However, as the cell membrane repolarizes and becomes more negative than the E_{rev} of SAC_{NS}, this can give rise to late AP prolongation (693), potentially resulting in a crossover of the repolarization curve (687).

The role of SAC_{NS} in causing the typical stretch-induced changes in cardiac electrophysiology is further supported by studies using pharmacological blockers (657) (although results must be interpreted with caution, as discussed in sect. III*D3*). Gadolinium (Gd^{3+}) and amiloride, two nonspecific blockers of SAC, have been shown to reduce the incidence of stretch-induced ectopy in ex vivo hearts (221, 245, 547), and to prevent stretch-induced changes in electrophysiology in myocyte monolayers (320), single myocytes (281, 556, 693), cardiovascular smooth muscle cells (670), and expression systems (217). More specific compounds have shown similar inhibition of stretch effects, such as streptomycin (20, 40, 150, 161, 192, 245, 320, 371, 423, 614, 644, 650), which at low concentrations serves as

a reasonably selective SAC blocker in vitro (657), and the selective SAC_{NS} inhibitor *Grammostola spatulata* mechanotoxin-4 (GsMTx-4) (28, 430, 492, 578, 641).

SAC_{NS} have also been implicated in mechanically-induced ventricular arrhythmias. In the rabbit isolated heart model of commotio cordis, it was shown that impact-induced excitation was dependent on SAC_{NS} (492), as it was blocked by GsMTx-4. This is in apparent contrast to results from an anesthetized pig model of commotio cordis, where streptomycin did not alter the probability of VF induction after precordial impact (193). The rabbit heart study, however, also showed no effect of streptomycin on mechanically-induced excitation (492), which may reflect the limited efficacy of streptomycin for acute SAC_{NS} block in native myocardium (119) (for a discussion of utility and limitations of SAC blockers, see sect. III*D3*).

During acute ischemia, a role of SAC_{NS} in stretch-induced excitation has been suggested by computational modeling (274). This is in contrast to recent experimental reports, where application of Gd^{3+} (25) or GsMTx-4 (28) did not alter the incidence of arrhythmias in whole animal (pig) experimental models. The interpretation of data from pharmacological intervention in whole animals is challenging, of course, as the lack of an observation of an effect is not the same as observation of a lack of an effect, given that pharmacological agents used to target SAC have a number of restrictions that affect their utility in vivo (discussed further in sect. III*D3*). In particular, Gd^{3+} has been shown to precipitate almost completely upon interaction with anions in physiological buffers, causing a drastic reduction in its free concentration (83), so that it cannot be recommended for in vivo MEC studies. In the pig experiments using GsMTx-4, the effective concentration at the level of cardiac cells would have been extremely low, given that the peptide is diluted not only in plasma (which would have yielded 170 nM, a concentration that has been found to be effective in some, but not all, in vitro studies), but also in interstitial fluid (which has a 3 times greater volume than plasma), yielding an effective concentration of GsMTx-4 of less than 50 nM; this may not have blocked SAC_{NS} effectively.

Along with SAC_{NS}, additional stretch-modulated mechanisms may contribute to arrhythmogenesis in acute ischemia (239), such as the stretch-modulated $I_{K,ATP}$ (acting as a K^+-selective stretch-activated channel, SAC_K) (627, 628), sympathetic stimulation (241), or altered Ca^{2+} handling (33). In particular, a role for mechanical augmentation of $I_{K,ATP}$ in ischemia is supported by the fact that preventing paradoxical segment lengthening of affected tissue in a pig model of myocardial ischemia using a mechanical splinting device delayed K^+ accumulation in the ischemic zone, and prevented electrophysiological changes such as APD shortening and occurrence of alternans (59).

In the atria, the importance of SAC_{NS} for stretch-induced excitation is supported by experiments showing that Gd^{3+} (which blocks $I_{SAC,NS}$ in isolated atrial cells; Ref. 698) suppresses ectopy (599). Indeed, in stretch-augmented rapid pacing-induced AF models, Gd^{3+}, streptomycin, and GsMTx-4 all reduce AF inducibility **(FIGURE 9*C*)**, without affecting refractoriness (55, 56, 179, 436). Interestingly, the stretch-mediated increase in AF inducibility can be reduced by altering the fatty acid composition of cardiac cell membranes with dietary fish oil, possibly by changing physical membrane properties and altering mechanical stimulus transmission from macroscopic input (pressure/volume overload) to SAC and stretch-modulated currents as molecular sensors (434).

There may also be a contribution of stretch-induced excitation, mediated via SAC_{NS}, in pulmonary vein automaticity, a key clinical contributor to AF. Here, stretch results in an increased incidence and rate of firing (278), which is blocked by Gd^{3+} and streptomycin (100) (although with Gd^{3+}, simultaneous block of I_{Na} may also contribute to suppression of excitation; Ref. 350). Streptomycin, on the other hand, can also block L-type Ca^{2+} channels (39), and Ca^{2+} influx via L-type Ca^{2+} channels may be one of the contributors to the decrease in refractoriness with atrial dilatation, as changes in refractoriness and AF inducibility are also prevented by block of $I_{Ca,L}$ (618, 691). Interestingly, a recent report has implicated caveolae-mediated activation of stretch-activated $I_{Cl,swell}$ as a critical cause of pulmonary vein automaticity with stretch; however based on the considerations of a role of $I_{Cl,swell}$ in a stretch-induced increase in automaticity discussed above, this finding requires further investigation (163).

2. SAC_K

While all of the known acute stretch-induced effects on cardiac electrophysiology in healthy myocardium can be reproduced in quantitative computational models by simply invoking $I_{SAC,NS}$, there is strong evidence supporting a contribution by SAC_K, specifically in ATP-deprived tissue. During systole, activation of SAC_K (whose E_{rev} is close to the reversal potential of K^+) would be expected to enhance APD shortening (297) and, if activated in resting cells, to hyperpolarize V_m. The latter has not been reported, which suggests that SAC_K do not dominate MEC responses in healthy cardiomyocytes. In ischemia, there may be an additional contribution to APD shortening by the stretch-modulated $I_{K,ATP}$ (627, 628). $I_{K,ATP}$ has additionally been implicated in VF induction in the setting of commotio cordis, as administration of the nonspecific $I_{K,ATP}$ blocker glibenclamide reduced the incidence of VF induction in pigs upon precordial impact (366). That said, under conditions of normal oxygen supply, $I_{K,ATP}$ is inactivated (441) and not responsive to mechanical stimulation (627, 628) (in fact, the combined sensitivity to stretch and ATP reduction may explain why, to cause channel opening in vitro, ATP concen-

trations must be reduced far more than might be expected to occur in vivo). In keeping with nonspecific effects of the blocker used (glibenclamide) (19, 501), the decrease in the incidence of mechanically-induced VF may instead represent pharmacologically-induced changes in repolarization timing and refractoriness, causing a shift in the exceedingly narrow vulnerable window for mechanically-induced reentry (492) and, hence, a potentially false-positive conclusion regarding glibenclamide effects on cardiac mechano-sensitivity. In the case of increased AF incidence with atrial dilatation, K^+ influx via SAC_K may contribute to decreased refractoriness, and it has been shown that acidotic conditions, which amplify stretch activation of K^+ channels such TREK-1 (378), cause an additional reduction in refractory period and increase in AF susceptibility with atrial dilatation (436).

3. Mechano-sensitivity of intracellular Ca^{2+} handling

Stretch directly affects intracellular Ca^{2+} handling in cardiac cells. Stretch has been shown to acutely increase SR Ca^{2+} release in guinea pig (257), rat (190, 258, 482), and mouse (481) ventricular myocytes, via either direct mechanical (258), ROS-mediated (481), or mitochondrial Ca^{2+}-related (36, 37, 405, 412) influences on RyR open probability, which may contribute to Ca^{2+}-induced afterdepolarizations (182). This stretch-induced increase in SR Ca^{2+} release may be especially important in acute ischemia as it is enhanced, along with the stretch-induced increase in ROS production, in that setting (90). Intracellular free Ca^{2+} is also acutely affected by a length-dependent change in the affinity of troponin C (TnC) for Ca^{2+} (4), such that with increased stretch (4, 6) or tension (685), more Ca^{2+} is in the bound state. Upon rapid shortening, the dissociation of Ca^{2+} from TnC causes a surge in intracellular Ca^{2+} (638). In this period RyR can have sufficiently recovered to allow additional Ca^{2+}-induced Ca^{2+} release from the SR (24), which can cause propagating Ca^{2+} waves **(FIGURE 18*A*)**. Cellular excitation may then occur (141, 605, 639) by depolarization of V_m via electrogenic Ca^{2+} removal through I_{NCX} (408). It is important to note that in the given example, it is the relaxation of stretched muscle, rather than the stretch per se, that causes this Ca^{2+}-mediated arrhythmic trigger. Such response would be in keeping with the observation that Ca^{2+} release is enhanced by increasing the rate of relaxation (639), independently of the involvement of SAC_{NS} (407). Importantly, in the case of nonuniformly contracting myocardium, for instance, with regional changes in contraction as occurs in ischemia or long QT syndrome, acute mechanically-induced changes in Ca^{2+} dynamics may give rise to arrhythmogenic Ca^{2+} waves (406, 603, 604, 606). These waves themselves can then result in aftercontractions that cause afterdepolarizations in other cardiac tissue segments, which may trigger tachyarrhythmias (188, 601) **(FIGURE 18*B*)**.

4. Summary

SAC_{NS} can explain most electrophysiological MEC responses in working myocytes of the heart. With an E_{rev} approximately halfway between peak AP and resting V_m, $I_{SAC,NS}$ can cause depolarization and excitation in resting cells, while during the AP plateau it can accelerate early repolarization and shorten APD. As a result, SAC_{NS} have been implicated in atrial and ventricular arrhythmogenesis, including settings such as AF, commotio cordis, or acute ischemia. These effects may be reduced or prevented by SAC_{NS} blockers, but they must be used with careful consideration to avoid erroneous conclusions. Other subcellular stretch-modulated components may also contribute to proarrhythmic stretch effects, such as afterdepolarizations, ectopic excitation, and tachyarrhythmias, including SAC_K (e.g., the stretch-modulated $I_{K,ATP}$) and intracellular Ca^{2+} handling (via changes in SR Ca^{2+} release or the affinity of TnC for Ca^{2+}).

C. Cardiac Non-Myocytes

1. SAC_{NS}

While electrophysiological responses to stretch in native cardiac tissue can be explained generally by direct MEC effects on myocytes, they may partially be mediated through mechano-sensitivity of electrically-coupled non-myocytes, such as macrophages [which have been shown to both express SAC_{NS} (455) and electrically couple to myocytes (247)] or fibroblasts (313). Fibroblasts are relatively depolarized cells that possess SAC_{NS} (573). They have been shown to form structural connexin-based links with SAN cells (89) that support active electrotonic coupling with cardiomyocytes (490, 529) in native tissue. In cell cultures, fibroblasts can act as current sinks that affect cardiomyocyte excitability, repolarization, and conduction (305, 404), and they may serve as passive conductors between structurally separate myocyte groups (196, 205).

Stretch has been shown to cause fibroblast depolarization (282, 315, 317), a response that is sensitive to pharmacological depletion or buffering of fibroblast intracellular Ca^{2+} (303), and that has been implicated in mechanically-induced electrophysiological changes in fibrotic cardiac tissue (610). A role for non-myocytes in stretch-induced electrophysiological responses may underlie the observation that the magnitude of mechanical effects on HR increases with structural complexity of the biological model: isolated SAN cells ~5%, whole-heart/SAN tissue ~15%, intact dog up to 30% (even though the inherent reduction in beating rate that occurs with more reduced preparations should have the opposite effect, i.e., the largest chronotropic response might be expected in isolated cells) (119). This phenomenon suggests a loss of contributory factors involved in transmission or sensing of mechanical stimuli, as one moves

towards more reduced biological model systems (which, in denervated preparations, will also include loss of autonomic nervous system contributions).

2. Summary

Mechano-sensitivity of non-myocytes, electrically coupled to cardiomyocytes, may contribute to MEC responses in the heart. Fibroblasts in particular have been shown to express SAC_{NS} and to electrically connect with cardiomyocytes, which may give rise to mechanically-induced changes in cardiac electrophysiology.

D. Molecular Candidates for SAC

1. SAC_{NS}

The first single-channel recordings of depolarizing $I_{SAC,NS}$ were reported in 1984 in cultured embryonic chick skeletal muscle (209). Since then, $I_{SAC,NS}$ has been recorded in isolated ventricular myocytes from various mammalian species, including human (133, 281, 283, 539). This current has a near-linear current-voltage relationship (as is typical for weakly selective ion channels), a single-channel conductance between 10 and 30 pS, and an E_{rev} somewhere between −20 and 0 mV. In contrast to atrial cells, where single-channel recordings of SAC_{NS} have been reported (300), SAC_{NS} channels in adult ventricular cardiomyocytes appear to be hidden from direct patch pipette access, for example in membrane regions of the transverse tubular system (244), caveolae, or at intercalated disks (264). Two principal families of candidates for SAC_{NS} have been identified: TRP and Piezo channels, both of which have been shown to be expressed in the plasma membrane of numerous human and animal cell types (476) **(FIGURE 19)**.

Most TRP channels found in mammals are cation nonselective, and depending on the specific channel, pass some com-

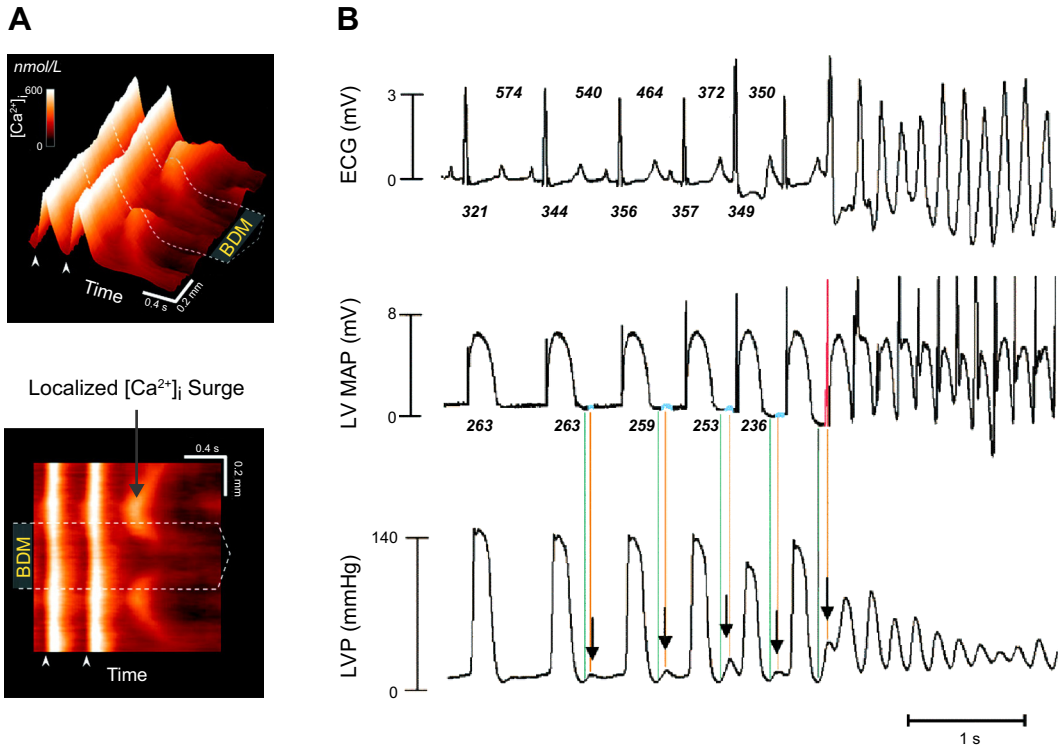


FIGURE 18. Effects of nonuniform mechanical activity on ventricular cardiomyocyte intracellular calcium concentration ($[Ca^{2+}]_i$), contraction, and electrical activity. *A*: three- (*top*) and two-dimensional (*bottom*) spatio-temporal representations of $[Ca^{2+}]_i$ showing electrically stimulated $[Ca^{2+}]_i$ transients (white arrows) in a rat ventricular trabecula, followed by a surge in $[Ca^{2+}]_i$ at the border between normal and weakened muscle [by perfusion with 2,3- butanedione monoxime (BDM) across the central part of the trabecula], triggering two propagating $[Ca^{2+}]_i$ waves. [Adapted from Wakayama et al. (638), with permission from Wolters Kluwer Health.] *B*: after-contractions of increasing amplitude during β-adrenergic stimulation in the left ventricle (see arrows in the *bottom trace*, left ventricular pressure, LVP) of an anesthetized dog model of acute long QT syndrome (induced by pharmacological inhibition of the slow component of the delayed-rectifier potassium current by HMR1556), preceding afterdepolarizations (blue segments in *middle trace*, left ventricle epicardial monophasic action potentials, LV MAP). These mechanically induced depolarizations eventually reach the threshold for ventricular excitation (red in LV MAP trace), triggering torsades de pointes (*top trace*, the electrocardiogram, ECG). Green and orange lines illustrate that onset and peak of LV aftercontractions, respectively, precede afterdepolarizations. [Adapted from Gallacher et al. (188), with permission from Oxford University Press.]

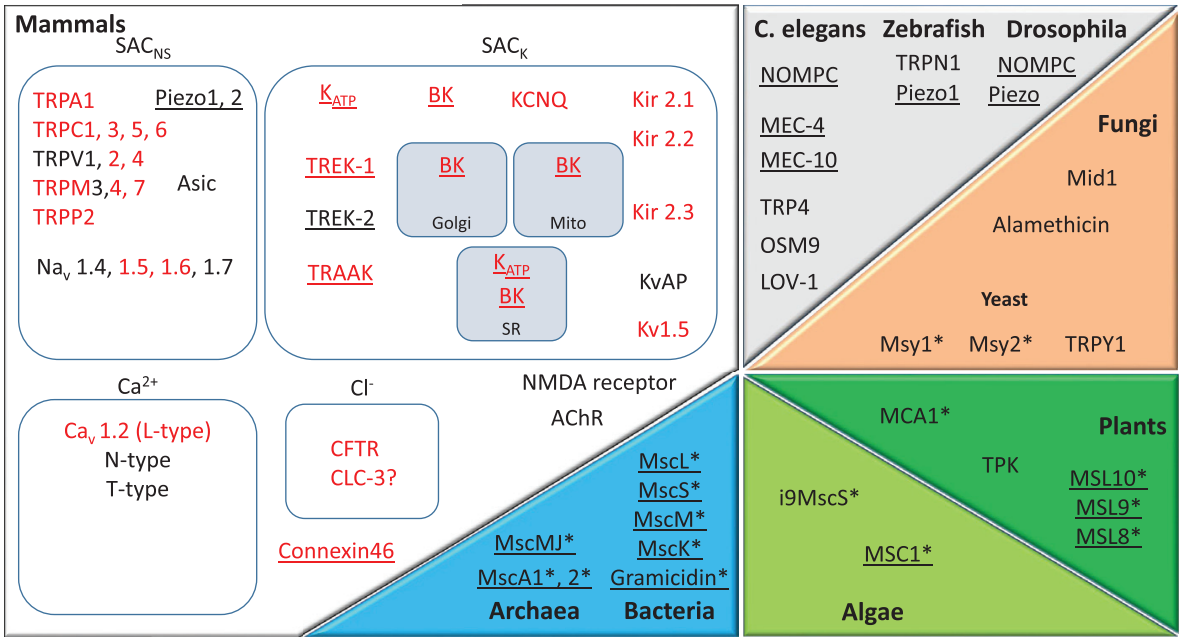


FIGURE 19. A selection of the more well-known mechano-sensitive ion channels and receptors in different organisms. Channels in red are expressed in the heart, underlined channels have been clearly identified as mechano-gated, while channels with an asterisk (*) have no known mammalian homologues. Examples of mammalian channels with homologues in other organisms include NOMPC, OSM9, TRP4, TRPY1, and LOV-1, which are transient receptor potential homologues; MEC channels, which are members of the degenerin/epithelial sodium channel superfamily that in mammals are Asic; TPK, which is a homologue of K_{2P} channels; and Mid1, which is homologous to voltage-gated calcium channels. AChR, acetylcholine receptor; Asic, acid-sensing ion channels; BK, big potassium (K^+) channels; CFTR, cystic fibrosis transmembrane conductance regulator; CLC, chloride channels; K_{ATP}, ATP-inactivated K^+ channel; KCNQ, KQT-like voltage-gated K^+ channel; LOV, location of vulva; Mid1, mating induced death; MCA, mechanosensitive Ca^{2+} channel; MSC, mechanosensitive channel of small-conductance homologue in *Chlamydomonas reinhardtii*; MscA, K, L, M, MJ, S, mechano-sensitive channel of archaeon, K^+, large, medium, *Methanococcus jannashii*, small conductance, respectively; Mito, mitochondria; MSL, mechansosensitive channel of small conductance like; Msy, MscS homologues in fission yeast; NOMPC, no mechanoreceptor potential C; NMDA, *N*-methyl-D-aspartate; SAC_{NS}, cation-nonselective stretch-activated channel; SAC_K, stretch-activated K^+-selective channel; SR, sarcoplasmic reticulum; TRAAK, TWIK-related arachidonic acid-activated K^+ channel; TREK, TWIK-related K^+ channel; TRPA, C, M, N, P, V, and Y, transient receptor potential ankyrin, canonical, melastatin, NOMP, polycystin, vanilloid, and yeast channels, respectively; TPK, 2-pore domain K^+ channels; OSM, OSMotic avoidance abnormal family; TWIK, 2-pore K^+ domains in a weak inwardly rectifying K^+ channel. [From Peyronnet et al. (476), with permission from Wolters Kluwer Health.]

bination of Ca^{2+}, Mg^{2+}, Na^+, K^+, and Cs^+. They are generally widely expressed and play a critical role in sensory physiology by enabling cells to sense changes in their local environment (including chemicals, temperature, osmolarity, vibration, and pressure). They can be activated by multiple factors, including mechanical stimuli [such as osmotic stress, shear force, and membrane stretch (255), although direct stretch activation of TRP channels is discussed controversially (432)]. Particularly interesting candidates for cardiac SAC_{NS} include members of the TRPC, TRP vanilloid (TRPV), TRP melastatin (TRPM), and TRP polycystic (TRPP) protein subfamilies.

In terms of candidates in the TRPC subfamily of channels, TRPC6 is highly expressed in the human heart (516), being localized in transverse tubules of mouse ventricular myocytes (160). Stretch activation of TRPC6 was first characterized in human embryonic kidney cells (566). Lack of mechano-sensitivity of TRPC6 expressed in Chinese hamster ovary (CHO) or monkey kidney fibroblast (COS) cell lines (206) may be attributed to the requirement for coexpression of angiotensin II receptor type 1 to yield SAC activity (255, 631). $I_{SAC,NS}$ in mouse cardiomyocytes during shear stress is reduced by pore-blocking TRPC6 antibodies or detubulation (160). TRPC3 expression has been shown in rat ventricular myocytes, where, like TRPC6, it is found in the transverse tubular system (183). In mouse neonatal cardiomyocytes, the channel is involved in ROS production upon mechanical stimulation or application of 1-oleoyl-2-acetyl-*sn*-glycerol (OAG), a nonspecific activator of SAC (183). Stretch activation of TRPC1 is controversial. It was initially demonstrated in *Xenopus* oocytes (386); however, like for TRPC6, it was not confirmed in other expression systems (206), suggesting that this channel may also require the presence of a partner protein. Caveolin 1 may be a trafficking regulator of TRPC1 (254, 458). As caveolae can

be integrated into the sarcolemmal surface membrane of ventricular cardiomyocytes in response to stretch (311, 477), TRPC1 mechano-sensitivity may be linked to stretch-induced changes in membrane topology, including knock-on effects on conduction velocity (due to a stretch-induced increase in membrane capacitance) rather than ion channel function of the protein.

With regard to candidates in other TRP subfamilies, TRPV2, expressed in the mouse heart (264, 531), is activated by patch pipette suction and cell volume changes (420), and it has been proposed to contribute to Ca^{2+} handling in cardiac cells (531). TRPM4 is expressed in cardiomyocytes of several species, including mouse, rat, and human (631), and it has been implicated in stretch-activated responses of vascular smooth muscle (414), although its physiological role in the heart is currently unknown. TRPP2 is primarily found on the endoplasmic/sarcoplasmic reticulum and in primary cilia (647), but a TRPP2-like protein seems to function as an ion channel in the sarcolemma of rat ventricular myocytes (634), potentially acting as a modulator of RyR activity (13).

The discovery of Piezo channels (Piezo 1 and 2) constituted a breakthrough in the field of mechano-transduction (127). Stretch activation of Piezo 1 has been demonstrated with heterologous expression in human embryonic kidney cells, resulting in $I_{SAC,NS}$ (128). While Piezo has not been detected at the protein level in cardiomyocytes, and no functional data have been published for Piezo in the heart at the time of writing (34), low-level Piezo1 mRNA expression (compared with lung, bladder, or skin) has been observed in mouse heart tissue homogenates (127). As Piezo current properties are similar to those of cardiac $I_{SAC,NS}$, including weak voltage dependency, single-channel conductance, inactivation, and sensitivity to GsMTx-4 (635), it is tempting to think that Piezo may indeed contribute to cardiac MEC. Whether this is through a direct involvement in cardiomyocyte function, or via non-myocyte-mediated effects (which would be in keeping with the low-level tissue homogenate mRNA data) remains to be elucidated.

2. SAC_K

A whole cell SAC_K current ($I_{SAC,K}$) in cardiac cells was first reported by Donghee Kim in 1992 (299). SAC_K is outwardly rectifying, allowing K^+ to move out of the cell more easily than in, has a relatively large single-channel conductance (~100 pS), and inactivates in a time-dependent manner. Single-channel $I_{SAC,K}$ recordings have been made in adult mammalian atrial (299) and ventricular myocytes (597, 643). $I_{SAC,K}$ is thought to be carried primarily by 2 P-domain K^+ channels (K_{2P}) in the mammalian heart (367) **(FIGURE 19)**.

One of the most studied K_{2P} channel is $K_{2P}2.1$ (TREK-1). TREK-1 is active over a range of physiological V_m and activated by a number of stimuli, including intra- and extracellular pH, temperature, fatty acids, anesthetics, and membrane deformation or stretch (46, 70, 236). TREK-1 in the rat heart is arranged in longitudinal stripes on the surface of cardiomyocytes, a pattern that could support directional stretch sensing (356a). TREK-1 shows heterogeneous expression in rat heart, increasing transmurally from sub-epi- to sub-endocardium (574, 596). This heterogeneity seems to correlate with transmural differences in mechanical sensitivity of myocardium, where stretch causes the most pronounced AP shortening in the sub-endocardium (203, 297). While TREK-1 mRNA expression has been reported in rat atria and ventricles (1, 367, 596, 607), it has not yet been identified in human heart (1, 211). Whole-cell currents exhibiting the characteristics of TREK-1, including sensitivity to internal acidification, anesthetics, and stretch, have been observed in atrial and ventricular myocytes of several mammalian species including rat, mouse, and pig (203, 544). TREK-1 contributes to the "leak" K^+ conductance in cardiomyocytes, aiding in repolarization and diastolic stability (203, 463). During stretch, increased K^+ current could cause excessive, pro-arrhythmic AP shortening (297). TREK-1 can be particularly pro-arrhythmic in patients with channel mutations. In a patient with right ventricular outflow tract tachycardia, a heterozygous point mutation in the selectivity filter of TREK-1 has been identified, which increased Na^+ permeability and mechano-sensitivity of the channel (145). TREK-2 shares functional similarity with TREK-1, is expressed in rat atria (367), and appears active in chick embryonic atrial myocytes (695), yet little is known about its functional relevance in the heart. The TWIK-related arachidonic acid-activated K^+ channel (TRAAK) is a TREK-1 homologue with similar biophysical properties and regulation (439). TRAAK is expressed in human heart (367, 454) and might form the human TREK-1 homologue, although its functional relevance has not yet been demonstrated.

There may also be a contribution to $I_{SAC,K}$ from big K^+ (BK) channels, which are activated by various stimuli and which therefore have been given multiple names (e.g., SAK_{CA}, BK_{Ca}, SLO1, MaxiK) (197). BK channels have a large conductance (100–300 pS), are present in many cardiovascular cell types, including vascular smooth muscle and atrial and ventricular cardiomyocytes (595). They are found in the sarcolemma, as well as in membranes of the endoplasmic reticulum, the Golgi apparatus, and mitochondria (197). Stretch activation of BK channels was observed in membrane patches excised from cultured embryonic chick ventricular myocytes (294). However, as BK channels are activated also by V_m changes and by intracellular Ca^{2+} (595), it has been suggested that their mechano-sensitivity may be indirect, occurring secondary to stretch-induced changes in intracellular Ca^{2+} concentration caused by $I_{SAC,NS}$ (256). In terms of their physiological role, BK channels have been suggested to contribute to HR control

(253) and to offer cardioprotection during ischemia (674), along with $I_{K,ATP}$.

3. Considerations for the use of pharmacological probes

Pharmacological modulators are among the most effective tools available for investigating molecular mechanisms of MEC (657). The principal agents for this are blockers and activators of stretch-modulated sarcolemmal ion channels. The most widely used probes in the heart to date have been two types of nonspecific inhibitors of $I_{SAC,NS}$: lanthanides and aminoglycosidic antibiotics, which have been highly productive for experimental cell research in vitro. Caution is needed, however, with their use, as limitations can lead to false-positive or -negative conclusions.

Lanthanides, most commonly Gd^{3+}, nonspecifically reduce $I_{SAC,NS}$ at concentrations of 1–100 μM. Their mechanism of action is thought to be multi-site, involving open-channel block of SAC_{NS} (178) and screening of surface negative charges, which alters the properties of the lipid bilayer (218). In isolated cardiac cells, they have been shown to block whole cell $I_{SAC,NS}$ in atrial (283, 698) and ventricular myocytes (261, 280, 281, 693), and to prevent the increase in subsarcolemmal Ca^{2+} during cell prodding (556). However, in preparations where $I_{SAC,NS}$ cannot be isolated from other currents, interpretation of results is difficult. Within the concentration range used to inhibit $I_{SAC,NS}$, Gd^{3+} is known to also inhibit $I_{Ca,L}$ (IC_{50} = 1.4 μM) (332), I_{Na} (IC_{50} = 48 μM) (350), I_{Kr} (although not I_{Ks} or I_{K1}) (462), and I_{NCX} (IC_{50} = 20–30 μM, depending on V_m) (697). Another important consideration is that fact that Gd^{3+} interacts with anions present in physiological buffers (HCO_3^-, CO_3^{2-}, HPO_4^{2-}, and PO_4^{3-}), forming precipitates that drastically reduce its free concentration (addition of 1 μM to solutions containing standard amounts of phosphate and bicarbonate results in a free Gd^{3+}concentration of less than 1 pM) (83). This can be a problem even with solutions employing synthetic buffers, if continually exposed to room air (as CO_2 dissolves in water, forming carbonic acid), and it will certainly alter available free Gd^{3+} in vivo.

Aminoglycosidic antibiotics are composed of two or more amino sugars joined to hexose by glycosidic links; they are thought to act on SAC by partial occlusion of the channel pore (666). The most commonly used compound is streptomycin. As for Gd^{3+}, streptomycin is not specific for SAC_{NS}, and it has been shown to also block Ca^{2+} and K^+ channels (39), as well as to reduce Ca^{2+} transients and contraction (38). In cardiac cells, it inhibits $I_{Ca,L}$ at relatively high concentrations (IC_{50} = 1–2 mM), but not at concentrations that inhibit $I_{SAC,NS}$ (40 μM) (40), demonstrating a superior demarcation between inhibition of SAC and other currents compared with Gd^{3+}, at least in vitro. "Pure" streptomycin has a molecular weight of 581.6 g/mol, but the most commonly available commercial form is streptomycin sulfate with a molecular weight of 1,457.4 g/mol. This requires an extra level of attention, as streptomycin concentration may differ by a factor of three if the wrong molecular weight is used for calculations (sadly, clear information needed to replicate experiments is not always provided; Ref. 491). A further consideration for the utilization of streptomycin is its limited utility for use in tissue (if streptomycin was an effective SAC blocker in vivo, it might not be suitable for prescription as an antibiotic). While it is an efficient blocker of SAC_{NS} in isolated or cultured cardiac cells (40), it has been shown to have a limited efficacy in native myocardium (119). This limitation results in the need for higher concentrations to affect stretch-induced responses (>200 μM) (161, 534) and in a disparity of positive and negative results, some of which may have been caused by lack of effect or off-target actions (492). It is also important to note that streptomycin (like other aminoglycosidic antibiotics) is a common component of standard cell-culture media, so caution is needed when interpreting studies on stretch effects in cultured cells, as background SAC_{NS} availability may be reduced in these preparations. Thankfully, streptomycin seems to wash off reasonably well in vitro (161, 534).

Among the more specific pharmacological agents for modulating SAC_{NS} activity, the best-known is the 35-amino acid peptide toxin GsMTx-4 (64). In particular, in its native (toxin-isolated) form, it has been shown to be a highly potent and specific inhibitor of $I_{SAC,NS}$ (578). GsMTx-4 has been shown to effectively block the stretch-induced increase in AF inducibility at a concentration of 170 nM (56) (2–3 orders of magnitude less than what is needed for similar effects by Gd^{3+} or streptomycin; Ref. 55), while showing no effects on AP shape at concentrations up to 4 μM (532). GsMTx-4 is an amphipath, having both hydrophobic and hydrophilic groups, and is thought to act by insertion into the outer leaflet of the sarcolemma in the proximity of SAC_{NS}, preventing mechano-sensing by the channel (579). This mechanism of action is not stereospecific or chiral, as both the D- and L-enantiomers of GsMTx-4 inhibit $I_{SAC,NS}$ (579). GsMTx-4 cDNA has been sequenced and a cloned 34-amino acid version of the wild-type toxin synthesized. In the hands of several investigators, the synthesized version has been found to require much higher concentrations (μM, not nM) to inhibit $I_{SAC,NS}$, potentially indicative of the difficulty in properly folding peptides ex vivo (453). It has been shown, though, that GsMTx-4 blocks the SAC_{NS} candidate proteins Piezo1 (22, 475) and TRPC6 (456, 566).

Specific activators [Yoda1 (334, 588); Jedi (645)] and inhibitors [Dooku1 (171)] of Piezo1 are now available, offering a potentially powerful new tool for determining whether Piezo1 is indeed a key player in cardiac MEC. Similarly, a number of activators and inhibitors of various TRP channels have been reported (174), which will be use-

ful in probing the role of those ion channels in tissue- and organ-level MEC.

Another interesting class of pharmacological probes for investigating subcellular mediators of MEC responses are those that target the cytoskeleton (657), although results have been inconsistent. Cytochalasin D, which prevents actin polymerization, has been shown to cause an increase in $I_{SAC,NS}$ in atrial myocytes (300), but similar results were not seen by others (698). Conversely, application of cytochalasin (280) and colchicine (which prevents microtubule polymerization) (261) causes a reduction in $I_{SAC,NS}$ in ventricular cells. On the other hand, the microtubule stabilizer paclitaxel has been shown to cause both an increase in the susceptibility to stretch-induced arrhythmias in rabbit isolated hearts (460) and a decrease during acute ischemia in rat isolated hearts (93), while inhibiting the stretch-induced increase in AF inducibility (673). Colchicine, however, had no effect (151, 460). Thus, overall, there is no general agreement regarding the role of the cytoskeleton in MEC effects. This lack of consensus may in part be due to the fact that, as with other pharmacological agents discussed above, actin and tubulin modulators are not specific to the cytoskeleton, and the degree to which they actually disrupt the cytoskeleton is rarely monitored (79). Also, the individual molecular components of the cytoskeleton may have their own, independent effects on intracellular Ca^{2+} handling and ion channel function (201, 202, 298), although this is debated (78, 80, 461).

4. Summary

While the electrophysiological consequences of stretching the heart have been well characterized, the molecular mechanisms involved are still unclear. In particular, the specific identities of cardiac SAC_{NS} and SAC_K in different cardiac cell types are largely unknown. Based on the biophysical characteristics of $I_{SAC,NS}$ and $I_{SAC,K}$ in cardiac cells, there are numerous candidates, including Piezo and various TRP channels (for SAC_{NS}), and K_{2P} channels such as TREK-1 and BK channels (for SAC_K). While pharmacological tools have been helpful in narrowing down ion channel contributions, agents have been limited in their specificity and applicability to whole heart and organisms, hindering progress; more reliable probes are emerging, and they will drive further insight into subcellular mechanisms of MEC.

E. Knowledge Gaps and Future Directions

- The molecular mechanism(s) responsible for the chronotropic response to SAN stretch are still unconfirmed, including the role of mechano-sensitivity of ion fluxes in SAN automaticity; targeted genetic and pharmacological studies are needed to address this fundamental aspect of cardiac function.
- It remains unclear how exactly the chronotropic response of the SAN to stretch differs between animal species; this requires comparative studies utilizing innovative approaches to determine underlying causes.
- Novel, more specific pharmacological agonists and antagonists are becoming available, which may lead to transformative insight into sarcolemmal and nonsarcolemmal SAC effects in normal homeostasis, pathogenesis, and therapy.

IV. INTEGRATIVE COMPUTATIONAL MODELS OF MEC

A. Single Cell

1. Consequences of SAC activation

In early computational studies of MEC, SAC currents were approximated either by simulation of currents with an appropriate E_{rev} through Ohmic conductances, i.e., as structures conducting charge not matter (ions) (315), or by an increase in background Na^+ and K^+ conductances (191). Since then, more detailed models of SAC have been developed, which include activation through biophysically-relevant parameters, allowing for simulation of stretch effects in cells, tissue, and whole hearts. In these formulations, SAC activation is scaled by either *1*) stretch (or strain) (227, 312, 693); *2*) stretch (or strain) rate (274); or *3*) tension (312), reflecting the lack of agreement on which biophysical input determines SAC activity. While these models have largely been successful in replicating known MEC responses, it is worth noting that even when they consider ion movements, they account for effects on bulk cytosolic ion concentrations only. If a subset of effectors interacted with physiologically-relevant subcellular compartments, such as submembrane spaces like the dyadic cleft, or with SR and mitochondrial Ca^{2+} stores, their influence on cardiac electrophysiology may not be captured by current models. This is true, also, for close proximity effects of mechanosensors, such as the putative secondary activation of BK channels in response to Ca^{2+} fluxes through colocalized SAC (256).

SAC incorporated into cardiac electrophysiology models have been used extensively in single cell simulation studies that recapitulate experimental data (307), occasionally in direct iteration with experimental studies. For instance, computational simulations correctly suggested that block of SAC with Gd^{3+} does not reduce the stretch-induced increase in resting Ca^{2+} in single ventricular myocytes, due to additional effects of Gd^{3+} on the delayed rectifier K^+ current and Ca^{2+} extrusion via I_{NCX} (235). Similarly, stretch effects on the delayed rectifier K^+ current, along with a transmurally varying $I_{SAC,K}$, were shown to plausibly explain transmural differences in AP changes upon stretch (227). Differences in experimentally reported stretch effects (including triggering of premature excitation and changes

in AP shape and duration) have also been explained by computational modeling, which suggested that the various responses relate to different subcellular mechanisms (for instance, SAC activation vs. changes in the Ca^{2+} affinity of TnC vs. modulation of SR Ca^{2+} handling) (312). These effects have been shown in cellular models to be further exasperated in conditions of Ca^{2+} overload, such as occurs with decreased activity of the Na^{+}-K^{+} pump (581).

The source of the experimentally established importance of stretch timing for cell-level responses has also been elucidated with computational simulations. That transient stretch, applied at the end of an AP or during diastole, causes depolarization and premature excitation, while stretch during the AP plateau causes early repolarization (and during later repolarization has little effect), can be explained by the interrelation of SAC_{NS} E_{rev} and cell V_m during those phases of the AP (312, 520, 688). Simulations have also demonstrated that this relation can explain the increase in beating rate of sinoatrial node cells with sustained stretch in rabbit (120), and that this stretch response may be enhanced by effects of SAC_{NS} activation in electrotonically-coupled fibroblasts (315, 317).

Not only does MEC result in premature excitation and enhanced automaticity, it may also modulate pro-arrhythmic electrical alternans. Computational simulations have shown that increasing $I_{SAC,NS}$ suppresses electromechanically concordant alternans (positive V_m-Ca^{2+} coupling or voltage-driven alternans), while it promotes electromechanically discordant alternans (negative V_m-Ca^{2+} coupling or Ca^{2+}-driven alternans) (187). In addition, the interaction of MEC with Mayer waves, involving oscillations in sympathetic nervous system activity and changes in ventricular preload, enhance this alternans promoting effect, which can ultimately result in premature excitation (484).

2. Consequences of altered intracellular Ca^{2+} handling

The increase in diastolic Ca^{2+} concentration, SR Ca^{2+} release, and TnC-Ca^{2+} affinity seen with stretch have all been reproduced in computational models. A stretch-induced increase in diastolic Ca^{2+} levels has been modeled on the basis of secondary effects of an increase in Na^{+} and K^{+} background conductances on I_{NCX} (191), highlighting the close interrelation of stretch effects on SAC and Ca^{2+} handling, the importance of identifying secondary effects of mechanical perturbations, and the relevance of further enhancing the 3D structural detail on subcellular compartmentalization of cardiac cells. The effect of stretch on SR Ca^{2+} release has been simulated by including, in a formulation of RyR Ca^{2+} flux, an exponential dependence on sarcomere length or tension (although the effect this has on cardiac electrophysiology was not investigated) (312). This has been extended to specifically simulate the stretch-induced increase in Ca^{2+} spark rate, linked to mechanically-stimulated ROS production, by developing an RyR model that includes a ROS-dependent mode switch (357). This model has also not yet been used to investigate the potential role this increase in Ca^{2+} spark rate may have on cardiac electrophysiology, but it has been used to make relevant predictions. Simulations using this model have demonstrated that stretch during diastole is expected to cause a local increase in ROS near the RyR complex, which increases the magnitude of the subsequent Ca^{2+} transient, potentially helping to match contractile force to hemodynamic load (290) and coordinating contraction across the heart (92). Furthermore, it has been suggested that when the chemical reducing capacity of cells is decreased, such as in ischemia, mechanically-stimulated ROS production contributes to global oxidative stress and enhances SR Ca^{2+} leak, which may increase the possibility of stretch-induced arrhythmias. Computational modeling has also suggested that the above effects may be microtubule dependent (275). These computational predictions, by and large, remain to be experimentally confirmed.

Stretch-induced changes in the Ca^{2+} affinity of TnC have been studied extensively, using computational simulations to understand effects on cardiac electrical activity (617). In the context of MEC, simulations have shown that with constant stretch, changes in TnC-Ca^{2+} affinity would be expected to delay repolarization, due to elevated Ca^{2+} buffering by TnC causing an increase in total SR Ca^{2+} release and a delay in reuptake that leads to an increase and prolongation of I_{NCX} (312, 429, 598). These stretch-induced AP changes differ from those predicted to arise from SAC activation, which, as described above, tends to cause AP shortening or crossover of the repolarization curve. Differences in the extent to which stretch effects are mediated by SAC or Ca^{2+} handling may therefore partly account for discrepancies in experimental findings of stretch effects on APD. This could be the case due to differences in timing or magnitude of applied stretch, differing (patho)physiological states, or unintended experimental influences (for example, the "clamping" of intracellular ion concentrations in whole-cell patch, as opposed to sharp electrode recordings). In fact, with stretch applied during the late plateau phase, TnC-Ca^{2+} binding (in contrast to SAC_{NS} activation) shortens the AP (312, 611), as the increase in Ca^{2+} buffering occurs at a time when SR Ca^{2+} release has terminated, thus reducing cytosolic Ca^{2+} concentration and I_{NCX} (312, 429, 598). The effects of mechanically-induced changes in TnC-Ca^{2+} affinity are also influenced by the mechanical state of the cell. Computational simulations suggest, for example, that increased cellular viscosity results in the occurrence of premature excitation due to an increase in intracellular Ca^{2+} levels, to the point of triggering spontaneous Ca^{2+} releases from the SR (289), and that Ca^{2+} overload and the ensuring incidence of arrhythmias can be enhanced by a decrease in the afterload imposed upon auxotonically contracting cells, or a decrease in preload for isometrically con-

tracting cardiomyocytes (288). Again, many of the modeling-based hypotheses in this context still await experimental validation.

3. Summary

Single cell computational simulations have been used successfully to reproduce observed MEC effects. This has helped in integrating and interpreting experimental data to elucidate underlying mechanisms, including the role of SAC_{NS} and SAC_K and of changes in intracellular Ca^{2+} dynamics or ROS, the importance of stretch timing, nonspecific effects of pharmacological agents, and the potential relevance of non-myocytes. That said, modeling of the effects of MEC at the cell level remains limited by a lack of fundamental information about characteristics of SAC function, such as mechanistic links between mechanical stimuli and channel opening, including their dependence on cytoskeletal elements and membrane properties such as tension and curvature, as well as three-dimensional distribution in highly structured cardiac cells, necessitating assumptions for model parameterization. This, of course, is a reflection of limits in experimental insight. Technological developments, such as membrane- (114) and protein-tension (125, 333, 681) sensors, their application to cardiac research, and improved 3D nano-scale reconstructions of cells (67, 523, 686), are needed to obtain and integrate the required information to further develop our conceptual and computational models.

B. Multicellular

1. Physiological mechanical activity and electrical instability

While single cell simulations are useful for recapitulating and explaining known cell-level MEC effects, tissue and whole organ simulations are necessary for exploring mechanically-induced changes in heart rate and rhythm that involve more integrative mechanisms. This aids in the understanding of causally-linked effects involving complex interactions between factors such as tissue composition and structure, electrophysiological and mechanical heterogeneity, and hemodynamics and organ geometry, while ideally allowing for the generation of novel experimentally-testable hypothesis and predictions (493, 616).

2D computational simulations of MEC have been used to investigate the effects of myocardial deformation caused by cardiac contraction. Theoretical studies have shown that contraction-induced deformation affects AP conduction, due to effects of tissue inertia (126) and stress-assisted diffusion (102, 369), which under pathological conditions can promote vulnerability to reentry (especially for curved wave fronts) (314, 654). This effect can lead to spiral wave breakup (457) and reduces the dispersion of repolarization between adjacent regions of interacting muscle (633). In addition, as in single cell simulations, stretch may influence electrical alternans, as computational simulations have demonstrated that SAC_{NS} can cause a transition from concordant (in-phase) to discordant (out-of-phase) alternations due to a change in the slope of the conduction velocity restitution curve (503), while spatially distributed stretch can instead suppress alternans (684).

3D computational simulations have also been useful for investigating experimentally intractable questions. For instance, 3D simulations have allowed examination of the importance of myocardial mechanics in MEC effects, suggesting that during ventricular loading AP changes are mediated by stretch in both the longitudinal and transverse myocyte axes (632), and that changes in conduction velocity are driven by reduced intercellular resistance and a concurrent increase of effective membrane capacitance (142, 403), for example, due to caveolar membrane integration. The stability of sustained transmural scroll waves, whose 3D organizational centers are only just becoming experimentally tractable (112), has been explored during stretch using biophysically detailed 3D electromechanical models of the ventricles. These demonstrated that MEC can cause deterioration of otherwise stable waves into turbulent patterns (296). In particular, wave stability depends on the E_{rev} and conductance of SAC: an E_{rev} of -60 mV reduces scroll wave breakup for all values of conductance by heterogeneously flattening the APD restitution curve, while an E_{rev} of -20 mV partially prevents scroll wave breakup at low conductance values by heterogeneously flattening the conduction velocity restitution curve (but not when conductance is increased, as I_{Na} inactivation in regions of large stretch leads to conduction block, counteracting the increase in scroll wave stability; Ref. 243). The putative impact of pathological states has also been investigated in a 3D electromechanical model of the ventricles, suggesting an increased importance of MEC effects in failing hearts (9).

2. Triggering and sustenance of arrhythmias

By their very nature, re-entrant cardiac arrhythmias require multiple electrically connected cells. A prime example of the utility of 2D and 3D computational modeling for the prediction of mechanisms underlying mechanically-induced reentry is commotio cordis. Simulating the application of a mechanical stimulus to a 2D sheet of ventricular myocytes by activating SAC_{NS} in a subpopulation of cells at different timings after the preceding "normal" wave of excitation (and therefore with differing overlap on the trailing repolarization-wave) demonstrated that SAC_{NS} causes depolarization in cells that have regained excitability, while it accelerates repolarization in cells at a V_m more positive than the E_{rev} of SAC_{NS}. Mechanical stimuli applied too early (i.e., when most of the tissue is still refractory) do not cause an excitatory response, while stimuli timed to occur well after a previous excitation, when most of the tissue is repo-

larized, trigger a single premature excitation. If, and only if, a mechanical stimulus overlaps the trailing edge of the previous wave of excitation, it may provide both a trigger (premature excitation) and sustaining mechanism (increased electrophysiological heterogeneity, including a functional block line at the intersection of the new and preceding excitation) for the development of sustained "figure-of-eight" re-entry (194) **(FIGURE 5*C*)**. This computationally-generated "overlap hypothesis" was corroborated in a 3D whole ventricle model by simulation of an epicardial mechanical stimulation, which added confidence to the original prediction and highlighted the fact that mechanical stimulus location (relative to the ventricular surface) is a variable that may affect the absolute timing (though not necessarily the duration) of the vulnerable window for VF induction (355). The modeling-based prediction that the vulnerable window for precordial impact-induced VF exists in time and in space gave rise to a subsequent targeted investigation, which experimentally confirmed the hypothesis 10 years later (492) **(FIGURE 6*E*)**.

A similar computational approach, using a combination of electrical trigger and subsequent mechanical stimulus in a 2D sheet of ventricular myocytes, has been utilized to model the stretch of mechanically weakened ventricular regions that occur in acute regional ischemia. In this case, when a mechanically-induced wave of excitation is initiated perpendicularly to an initial excitation after that has propagated through almost the entire sheet of tissue, the mechanically-induced excitation interferes with the trailing end of the original excitation, causing formation of a "spiral" re-entrant wave (similar to the arrhythmic effect of a critically-timed S1-S2 stimulus) (517). Alternatively, when a centrally located area of ischemic tissue is simulated, the wave of sinus excitation is slowed in the ischemic area, causing the formation of two wave fronts that circumvent the ischemic region. In this case, subsequent contraction of the surrounding myocardium that distends the ischemic tissue (paradoxical segment lengthening) may lead to SAC_{NS} activation and a mechanically-induced ectopic beat (314). These effects of acute ischemia may in fact be increased in diseased hearts where fibrosis is present, through mechano-sensitive fibroblasts, as computational simulations suggest that relatively small fibroblast-rich tissue and low levels of fibroblast-myocyte coupling may be sufficient to give rise to stretch-induced excitation in ventricular muscle (317, 694). As for studies of commotio cordis, the computationally-derived concept that stretch of the ischemic border zone during acute regional ischemia may be responsible for mechanically-induced excitation and re-entry has been supported by 3D computational modeling, which further showed that a combination of MEC and ischemic effects is necessary for the induction of ventricular tachyarrhythmias: when SAC_{NS} are omitted from the model, ectopic excitation and block of conduction do not occur, while when ischemia-induced electrophysiological changes are absent, the mechanically-induced ectopy and conduction effects do not result in re-entry (274) **(FIGURE 7*C*)**. Computational modeling further suggests that an increase in intraventricular volume during acute ischemia can result in ectopic excitation from the more compliant ischemic region (314), which has since been shown experimentally (459).

3. Modifying and terminating arrhythmias

In the case of sustained arrhythmias, MEC can affect re-entry dynamics. 2D computational simulations involving a fully coupled electromechanical model have been used to investigate mechanisms underlying the increased prevalence of VF in the mechanically compromised heart. These studies suggest that sustained stretch shortens APD and flattens the APD restitution curve. Stretch applied specifically near an excitation wave front, however, creates a distribution of stretch during spiral re-entry that is characterized by a large gradient at the core of the spiral wave, which then prolongs APD and creates an extended refractory region at the wave-end. This localized effect facilitates wave breakup and the occurrence of VF (231). In terms of atrial arrhythmias, computational simulations have suggested that MEC affects spiral wave frequencies, trajectories, and stability in AF (69), acting as a major source of cycle length variability during atrial flutter through effects of both respiration (as with respiratory sinus arrhythmia) and ventricular contraction, as atrial flutter interval (time between consecutive atrial activations) becomes phase-locked to ventricular contraction during periodic ventricular pacing (388).

The mechanisms by which mechanical stimulation may instead terminate established re-entry have also been investigated with computational modeling of precordial thump. When a mechanical stimulus is applied to a simulated 2D sheet of tissue in which sustained re-entry is occurring, activation of SAC_{NS} causes depolarization of excitable tissue and, if stretch is large enough, initiation of excitation in these regions. If the proportion of simulated tissue in which stretch eradicates the excitable gap is large enough, this will terminate the re-entrant wave (310). In cases of established VF however, the myocardium will often be in an ischemic state, due to diminished coronary blood flow, resulting in co-activation of stretch-modulated $I_{K,ATP}$. Computational modeling suggests that the combined activation of SAC_K and SAC_{NS} during mechanical stimulation will result in a more negative E_{rev} of the overall stretch-induced current, compared with control conditions (-35 vs. -10 mV). This reduces excitable gap depolarization, prevents formation of ectopic foci, and shortens APD (310), thus explaining one possible mechanism underlying the reduced efficacy of precordial thump in severely hypoxic hearts (675). MEC may also play a role in reducing the efficacy of electrical defibrillation in the arrested, volume-overloaded heart. 2D computational simulations have demonstrated that SAC_{NS} activation in this setting results in a more positive V_m at the end of the effective refractory period, a reduc-

tion in conduction velocity of shock-induced break excitations, and an increase in the complexity of post-shock VF patterns. This leads to a flattening of the defibrillation dose-response curve and an increase in the defibrillation threshold (210, 615).

Again, as for the examples of computational modeling of arrhythmia triggering, for the case of sustained arrhythmia termination by precordial thump, 3D results are similar to the 2D case, demonstrating that in the whole ventricle mechanical stimulation can obliterate excitable gaps, thus terminating the arrhythmia, and that the efficacy of this intervention is reduced by ischemia (356). Similarly, the reduced efficacy of electrical defibrillation due to SAC_{NS} activation shown with 2D modeling has been replicated in a 3D electromechanical model of the acutely volume overloaded ventricle (354).

4. Summary

Multicellular computational models have been an effective means for quantitative theoretical exploration of integrated (patho)physiological MEC responses, especially mechanisms of mechanically-induced and -terminated tachyarrhythmias, such as in the setting of commotio cordis, acute regional ischemia, and precordial thump. These simulations have predicted the critical importance of the relation of mechanical stimulation to underlying electrical activity for (anti)arrhythmic outcomes, generating novel hypotheses that have since been experimentally verified. Moving forward, continually increasing computational power, combined with advances in experimental insight, will make 2D and 3D simulations an increasingly compelling tool for studies of MEC.

C. Knowledge Gaps and Future Directions

- Computational models continue to increase in complexity and sophistication, but they often do not include MEC; this should become standard practice for relevant studies of cardiac structure and function.
- Much of the fundamental information needed for the effective development and parameterization of computational models that include MEC is still lacking; nonetheless, simulations of known MEC effects have been informative in identifying key knowledge gaps.
- Experimental and computational research should be conducted in close collaboration, using computational simulations to interpret and integrate experimental data, to generate novel experimentally testable hypotheses and predictions, and to guide experimental investigations that test these theories and suggestions, providing novel input data for computational model refinement.

V. SUMMARY AND CONCLUSIONS

In this review, we hope first and foremost to have conveyed the critical role of cardiac mechano-sensitivity in the autoregulation of the heart's electromechanical activity, and the vital importance of MEC in the acute adaptation of cardiac electrical behavior to changes in the mechanical environment. The feedback from mechanics to electrics is essential for the maintenance of normal HR and rhythm. In cardiac pathologies, however, MEC can contribute to the initiation and maintenance of arrhythmias, both in acute and chronic disease states. Finally, and very much like electrical current delivery to the heart, MEC can have not only arrhythmogenic effects, but also contribute to heart rhythm restoration.

Almost all clinical and experimental observations of MEC in the heart can be explained quantitatively by invoking no other mechanism besides SAC_{NS} in cardiac myocytes. However, one should be wary of the plausibility trap: simply because one mechanism may explain a response does not mean that said mechanism is the major driver of a response, or even involved at all. The mechanical modulation of other ion channels, as well as of intracellular Ca^{2+} handling and other signaling mechanisms (e.g., ROS), matters for MEC in healthy and diseased myocardium. In addition, mechanosensitive non-myocytes in the heart may play important roles in MEC effects. This complexity, along with our lack of understanding of the role and interplay of many molecular sensors and information pathways involved in MEC, leaves much to be discovered.

MEC studies are hampered by several experimental limitations, such as our inability to measure local tension inside cardiac tissue, and by the lack of selective pharmacological probes that can block or activate individual relevant players in native tissue, ideally in a cell-type specific manner. This restricts our ability to link discrete islands of insight at molecular, cellular, tissue, organ, and organism levels, and to project between species. At times, the setting reminds one of the famous "street-light effect" (284), where one looks for missing items not where they are most likely to be found, but where it is most convenient to search for them. That said, bridges can be built between experimentally-intractable questions and theoretical explanations using computational models to quantitatively assess the plausibility of interpretations and novel hypotheses, and to design new experimental research.

Finally, even based on our current partial understanding of mechanisms and roles of cardiac MEC in health in disease, it is clear that exciting potential for therapeutic interventions exists, for instance in the use of mechanical stimulation for heart rhythm management, in controlling mechanical modifiers of electromechanical structure and function, and in pharmacological targeting of subcellular players as novel means for anti-arrhythmic therapies. Overall, the current state of cardiac MEC research warrants further investigation into acute mechanical effects on HR and rhythm, to

help us come closer to a comprehensive understanding of the integrated electromechanical crosstalk that makes the heart tick in health and disease.

GLOSSARY

ATP-sensitive potassium current ($I_{K,ATP}$)	A potassium channel that is activated by a reduction in intracellular adenosine triphosphate and modulated by stretch.
Atrial fibrillation (AF)	Rapid, irregular excitation of some or all of the atria.
Bradycardia	Slow heart rate.
"Calcium (Ca^{2+}) clock"	Intracellular calcium cycling contribution to sinoatrial node automaticity.
Commotio cordis	Mechanical "agitation of the heart" (Latin), usually by a precordial impact of subcontusional energy, that may give rise to heart rhythm disturbances of varying severity and duration, including ventricular fibrillation.
E_{rev}, reversal potential	Membrane potential at which there is no net flow through an ion channel.
Gadolinium (Gd^{3+})	Chemical element that is a nonspecific blocker of cation-nonselective stretch-activated ion channels.
Grammostola spatulata mechanotoxin-4 (GsMTx-4)	Peptide isolated from the venom of the *Grammostola rosea* spider that is currently the most selective blocker of cation-nonselective stretch-activated channels.
I_f, "funny" current	Hyperpolarization-activated depolarizing "inward" current passed by cyclic nucleotide-gated channels, for example, in sinoatrial node cells.
Long QT syndrome	Condition in which repolarization of (part of) the ventricles is delayed, causing an increase in the QT interval of the electrocardiogram.
Maximum diastolic potential	Most negative membrane potential reached by pacemaker cells during their spontaneous cycle of de- and repolarization.
Maximum systolic potential	Most positive membrane potential reached by pacemaker cells during their spontaneous cycle of de- and repolarization.
Mechano-electric coupling (MEC)	Acute feedback from the mechanical status of the heart to its electrical activity.
"Mechanics clock"	System of mechano-sensitive mechanisms that contributes to sinoatrial node automaticity.
Precordial thump	A single fist impact, generally applied to the left of the lower half of the sternum, to reset disturbed heart rhythms.
Respiratory sinus arrhythmia	Physiological fluctuation in heart rate that is synchronous with the respiratory cycle.
Sinoatrial node (SAN)	A region of tissue in the right atrium that contains the primary cardiac pacemaker.
Spontaneous diastolic depolarization	Automaticity-providing shift in membrane potential in cardiac pacemaker cells.
Stretch-activated channel (SAC)	Ion channel that is gated by a mechanical stimulus (in the absence of cell volume changes).
Stretch-modulated channel	Ion channel whose activity is altered by a mechanical stimulus.
Tachyarrhythmia	Abnormally rapid heart rhythm.
Ventricular fibrillation (VF)	Rapid irregular excitation of the ventricles.
"Voltage (V_m) clock"	System of sarcolemma-bound ion flux mechanisms that contributes to sinoatrial node automaticity.
Vulnerable window	A narrow period during which the heart is particularly susceptible to the induction of arrhythmias.

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