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Cardiac Mechano-Gated Ion Channels and Arrhythmias

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Abstract

Mechanical forces will have been omnipresent since the origin of life, and living organisms have evolved mechanisms to sense, interpret and respond to mechanical stimuli. The cardiovascular system in general, and the heart in particular, are exposed to constantly changing mechanical signals, including stretch, compression, bending, and shear. The heart adjusts its performance to the mechanical environment, modifying electrical, mechanical, metabolic, and structural properties over a range of time scales. Many of the underlying regulatory processes are encoded intra-cardially, and are thus maintained even in heart transplant recipients. Although mechano-sensitivity of heart rhythm has been described in the medical literature for over a century, its molecular mechanisms are incompletely understood. Thanks to modern biophysical and molecular technologies, the roles of mechanical forces in cardiac biology are being explored in more detail, and detailed mechanisms of mechano-transduction have started to emerge.

Mechano-gated ion channels are cardiac mechano-receptors. They give rise to mechano-electric feedback, thought to contribute to normal function, disease development, and, potentially, therapeutic interventions. In this review, we focus on acute mechanical effects on cardiac electrophysiology, explore molecular candidates underlying observed responses, and discuss their pharmaceutical regulation. From this, we identify open research questions and highlight emerging technologies that may help in addressing them.

Cardiac electrophysiology is acutely affected by the heart's mechanical environment. Mechano-electric feedback affects excitability, conduction, and electrical load, and remains an underestimated player in arrhythmogenesis. The utility of therapeutic interventions targeting acute mechano-electrical transduction is an open field worthy of further study.

Keywords

heart; mechano-electric feedback; stretch-activated channels; heart rhythm

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1. Introduction to Cardiac Mechano-Sensitivity

History and Scope

The heart's propensity to respond to mechanical stimuli with acute changes in its activity has been known for centuries. Early reports in the European medical literature describing mechanical effects on human heart rhythm date back to the 19th century, such as the communications by Auguste Nélaton and Felice Meola^{1, 2} on sudden death caused by precordial impact.^{3, 4}

At about the same time, Oskar Langendorff⁵ developed his isolated perfused heart model which, by the way, offers vivid illustrations of mechano-sensitivity (e.g. touch-induced ectopy). Building on the Langendorff-method, physiologists like Henry Bowditch, Joseph Coats and Elias Cyon⁶ described effects of cardiac volume loading on contractility, nowadays commonly credited to subsequent defining work by Otto Frank and Ernest Starling.^{7, 8} Astonishingly, given the long history and vast importance of this mechano-mechanical feedback for auto-regulation of cardiac output, the mechanisms underlying the 'Frank-Starling Effect' are still subject of debate.⁹

In parallel, first experimental evidence of mechano-*electrical* feedback (MEF)¹⁰ was reported by Francis Bainbridge, who showed that stretch of the right atrium, containing the heart's primary pacemaker tissue, increases spontaneous beating rate.¹¹ This 'Bainbridge effect' is seen in the denervated heart, including human transplants,^{12–14} *ex situ* animal hearts,^{15–17} isolated tissue,^{18, 19} and even single isolated pacemaker cells,²⁰ highlighting the intrinsic nature of at least some of the underlying mechanisms. Conceptually related MEF effects are seen in cardiac myocytes^{21–24} and non-myocytes,^{25–27} highlighting the potential relevance of cardiac MEF for heart function (for more detail on MEF, see ²⁸).

This review will focus on one of the contributors to mechanically-induced acute changes in cardiac electrophysiology. Their effects are instantaneous, as opposed to more slowly occurring mechanical modulation of contractility, or even longer-term mechanically-induced changes in gene expression and cell/tissue remodelling. Several mechano-sensors of potential relevance for acute MEF responses have been identified. They include enzymes (e.g. mechano-sensitive kinases), structural elements from molecules (e.g. cytoskeletal and trans-membrane linkage-proteins) to membrane domains (e.g. caveolae) or more complex assemblies (e.g. contractile filament lattice and z-disks), but of particular interest are ion translocation mechanisms afforded by Mechanically Gated Channels (MGC).

MGC may serve both as sensors and as effectors of MEF responses. Embedded in membranes, they convert mechanical stimuli, putatively including in-plane membrane tension, membrane thickness and curvature, as well as matrix-protein interactions, into electrical and biochemical signals. MGC can affect, therefore, a wide range of cellular processes, with response times in the millisecond-domain relevant for acute cardiac MEF.

MGC were discovered in 1984 by the team of Frederick Sachs in embryonic chick skeletal myocytes.²⁹ Four years later, William Craelius and co-workers published the first MGC recordings from mammalian cardiomyocytes.³⁰ Since then, in addition to stretch-activated

whole-cell currents, single-channel activity has been identified in a wide range of cardiac cells,³¹ including atrial myocytes,³² foetal³⁰ and (for potassium selective MGC at least) adult ventricular myocytes,³³ as well as cardiac non-myocytes.²⁷

In the 1990s, the first MGC was cloned from *Escherichia coli* (MscL (Mechano-sensitive channel of Large conductance)),³⁴ and the molecular nature of the first mammalian MGC reported.³⁵ Since then, an increasing number of MGC has been identified and a large proportion of them are expressed and functional in the heart (Figure 1).

Since block of MGC in the mammalian heart can prevent certain forms of mechanically-induced heart rhythm disturbances in the experimental setting,^{36, 37} they form a putative therapeutic target. This has motivated the present assessment of what we know about them so far.

Channel Activation: Mechanical Modulation vs. Mechanical Gating

Mechanically Modulated Ion Channels vs. Mechano-Gated Ion Channels—Ion channels, relevant for MEF, are characterised by their ability to change open probability in direct response to mechanical stimulation. Traditionally, mechanically gated ion channels have been classed according to the stimulus by which they were activated (e.g. cell volume activated channels, stretch activated channels; Figure 2). However, it is difficult to apply perturbations in a way that alters only *one* mechanical parameter, even if techniques for controlled mechanical stimulation of membrane patches have improved.^{38–40} In this paper, we refer to MGC as channels that can be activated by a mechanical stimulus *alone*. Channels that are normally activated by a different type of stimulus, but with a gain that is affected by the mechanical environment, or those that require co-activation by non-mechanical stimuli, will be referred to as Mechanically *Modulated* Channels (MMC).

An example of MMC are channels normally classed as voltage gated—These include potassium,⁴¹ calcium,^{42–44} and sodium^{45, 46, 47} channels. Mechanical modulation of Kv channels (K⁺ channel, Voltage-gated) ranges from mechanically-induced redistribution (e.g. integration of Kv1.5 channels into the sarcolemma of rat atrial myocytes),⁴⁸ to direct stretch-induced gating (e.g. of Kir channels [K⁺ inwardly-rectifying channel] in murine ventricular myocytes).⁴⁹ Similarly, voltage-sensitive sodium channels can be affected by the mechanical environment (such as Na_v1.5 [Na⁺ channel, voltage-gated] in HEK [Human Embryonic Kidney] cells).⁵⁰ Modification of the channel stability at the membrane is another type of modulation and has recently been exemplified for the L-type calcium channel: Polycystin-1, well-known to act as a mechanosensor in several cell types, can stabilise the entire pool of L-type channel proteins in rat cardiomyocytes.⁵¹

Mechanical modulation of voltage-sensitive channel gating is perhaps less surprising than often assumed, given that voltage sensing requires conformational rearrangements of the channel protein.⁵² If channel opening is associated with an increase in protein dimensions in the membrane plane, then the open state should be favoured by increased membrane tension. That said – the precise conformational changes of many ion channels are not known, and it is clear that not all channels are mechano-sensitive in standard experimental conditions (for example TASK channels).⁵³

Ligand-activated MMC—GABAA (gamma-aminobutyric acid) and P2X (purinergic) receptors (P2X₃ and P2X₄ subtypes in particular), are both expressed in the heart, though not in cardiomyocytes but in neurons and smooth muscle cells, respectively.^{54, 55} They were suggested to participate in mechano-transduction processes, but their direct mechano-sensitivity remains to be established. P2X₄ is not activated by shear stress alone, and their role in mechano-transduction is suggested to stem from the ATP release that can be mechanically induced by them, as shown in endothelial cells.⁵⁶

Sarcolemmal K_{ATP} channels (K⁺ channel, ATP-inactivated), discovered in cardiac myocytes in the early 1980s,⁵⁷ are sensitive to their mechanical environment.⁵⁸ These K_{ATP} channels are hetero-octamers comprising two subunits: the pore-forming subunit with two membrane-spanning regions (Kir6.1 or Kir6.2 [K⁺ inwardly-rectifying channel]), and the regulatory subunit sulfonylurea receptor (SUR1, SUR2A, or SUR2B).^{59, 60} K_{ATP} are highly expressed in atrial and ventricular cardiomyocytes of murine models^{61, 62} and in human heart.⁶³

In normal metabolic conditions, K_{ATP} channels are inactivated. If ATP levels fall, K_{ATP} open probability increases. In the presence of stretch, this increase occurs at less reduced ATP levels.⁶⁴ This may explain the difference between *in vitro* studies (where ATP levels have to be severely reduced to open K_{ATP}) and the *in vivo* setting (where stretch of cardiac tissue is present at all times, and presumably elevated in regions with reduced ATP). It is thought that K_{ATP} channels are gated by local bilayer tension, and that this is affected by the cytoskeleton.⁶⁵

K_{ATP} channels may have a protective role in ischaemia.⁶⁶ Interestingly, stretch-preconditioning, known to reduce ischaemia-reperfusion injury, is abolished by blocking K_{ATP} channels.⁶⁷ Of note, cardiac K_{ATP} channels are also present and active in fibroblasts, suggesting that one must consider cardiac pre-/post-conditioning effects on cells other than just cardiomyocytes.^{68–70} As with other K⁺ channels, K_{ATP} opening favours re-/hyperpolarization. While beneficial in preventing spurious excitation of resting cells, this also shortens the action potential (AP) duration (APD) and reduces the refractory period. The latter could help to establish an arrhythmogenic substrate and support re-entry.

Channel Activation: Cell Volume vs. 'Stretch'

Cell Volume-Activated Channels (VAC) are generally regarded to be MGC—

That said, their mechanism of activation in the heart is poorly understood. What is known is that increases in cell volume, whether by swelling⁷¹ or pipette-based cell inflation⁷², tend to activate chloride⁷¹ or potassium conductances.³² While cell volume changes undoubtedly cause mechanical deformation, VAC-activation tends to occur with significant lag-times (tens of seconds to minutes) after the onset of cell volume changes.⁷³ This has put into question the role of direct mechanical stimuli as drivers of VAC gating, and it has been suggested that swelling-induced changes in cytoskeletal structures must take place before mechano-sensitive electrophysiological responses are seen.⁷⁴

In terms of patho-physiological settings, cell swelling can be observed in ischaemia, particularly upon reperfusion,⁷⁵ and VAC are understood to affect cardiac electrical

behaviour in these conditions. Interestingly, VAC-like Cl^- conductances are constitutively activated in hypertrophied cardiomyocytes,⁷¹ lending credence to the notion that structural aspects of cardiomyocyte organisation matter. Recently, LRRC8A (aka SWELL1), has been identified by two independent groups as an essential component of the ubiquitous volume-regulated anion channels VRAC.^{76, 77} This discovery has been a result of genome-wide RNAi screens, and provided a new molecular candidate to better understand cell volume regulation.

At the same time, the normal cycle of cardiomyocyte contraction and relaxation is not generally assumed to be associated with pronounced changes in cell volume. This, and the lag-time for VAC activation, make it unlikely that these channels are main contributors to acute, beat-by-beat MEF (for more information on cardiac VAC, see⁷¹).

Stretch-Activated Channels (SAC) – ‘the’ quintessential MGC—SAC increase their open probability in direct response to membrane deformation. Evidence demonstrating that lipid bilayer forces are sufficient to gate SAC was obtained for several bacterial, fungal,⁷⁸ and two vertebrate channels, TREK-1 (TWIK-related K^+ channel with TWIK standing for Tandem of two-pore K^+ domains in a weak inwardly rectifying K^+ channel) and TRAAK (TWIK-related arachidonic acid-activated K^+ channel).^{79, 80} The small number of channels tested in this way is caused in part by technical difficulties to purify or produce functional channel reconstitutes in pure lipid bilayers. Also, several SAC are likely to require cytoskeletal and linker-proteins,⁸¹ and/or possibly soluble factors or messengers for activation.⁸² Interestingly, mutations in cytoskeletal proteins have been linked to cardiac pathologies,^{83–86} including rhythm disturbances,^{87, 88} though thus far this would not appear to act via effects on MGC, but rather through effects on voltage-dependent channels and transporters that indirectly affect cardiac excitation-contraction-coupling. Several biophysical models have been proposed to address energetic interactions at the membrane-protein interface and contributions of lipid organization or, in addition to in-plane stress, changes such as membrane thinning have been suggested as relevant atomistic-level stimuli.^{89–91} These models, mainly obtained from bacterial channels reconstituted in liposomes, suggest that MGC can be gated by forces from lipids in the range of hundreds of pN (220 pN for MscL for example).⁹² More broadly, including eukaryotic channels in the cellular context (i.e. in the presence of the cytoskeleton), it appears that MGC are sensitive to a wide range of force intensities characteristic for living cells, *from 2 to 10 mN/m (data acquired on cultured cells)*.^{93, 94} To understand the mechanical gating of SAC, structural data is needed. So far, the structure of the bacterial MscL⁹⁵ and MscS (Mechano-sensitive channel of Small conductance),^{96, 97} as well as of mammalian TRAAK⁹⁸, Piezo1⁹⁹ and BK (Big K^+)¹⁰⁰ channels has been resolved at atomic resolution.

Channel Location: Sarcolemmal vs. Non-Sarcolemmal

Sarcolemmal MGC—Single channel patch clamp investigations require direct access of the pipette tip to the membrane containing channels, such as MGC. As the outer surface of the sarcolemma is easily accessible, it is the membrane from which most electrophysiological MGC data have been reported, so much so, that the notion of MGC seems synonymous with ‘sarcolemmal ion channel’. However, not all sarcolemmal channels

are present at the accessible cell surface, as ‘hidden’ cell surface membrane, such as in T-tubules (T-tub) and caveolae, contains ion channels.¹⁰¹ In addition, MGC are present also on endo-membranes of organisms such as plants¹⁰² and yeast,¹⁰³ and there is evidence to suggest that the same may hold true for mammalian heart cells.^{21, 104} Apart from BK channels, which appear in a range of endo-membranes and whose mechano-gating is discussed controversially (see section on BK channels, below), the following MGC are interesting examples that warrant further investigation.

Non-Sarcolemmal MGC: Sarcoplasmic Reticulum (SR)—Calcium handling in cardiac cells is mechano-sensitive, involving mechanisms from changes in Ca^{2+} buffering and troponin-C binding, to Ca^{2+} fluxes.^{105, 106} This includes Ca^{2+} releasability from the SR, such as evident in an increased frequency of SR Ca^{2+} release events (sparks) upon acute mechanical stimulation, whether using axial cell stretch or local application of fluid ‘puffs’ to deform isolated cells.^{21, 104} Mechanisms underlying the stretch-induced increase in spark rate continue to be investigated and may include mechanical modulation of RyR (Ryanodine Receptor) Ca^{2+} release channels of the SR.

This could have functional relevance not only for priming SR Ca^{2+} release and/or terminating it upon successful cell shortening, but it would also have the potential of affecting cardiac electrophysiology. If stretch triggered Ca^{2+} release from the SR, this could affect trans-sarcolemmal $\text{Na}^+/\text{Ca}^{2+}$ exchange and – in particular in cells that are already Ca^{2+} overloaded (e.g. in ischaemic conditions) – trigger ectopic excitation.³⁴

Non-Sarcolemmal MGC: Other Organelles—Mitochondrial K_{ATP} channels contribute to ischemic pre-¹⁰⁷ and post-conditioning,^{108, 109} potentially protecting cells by maintaining ATP production during hypoxic episodes.¹¹⁰ While the molecular identity of the cardiac mitochondrial K_{ATP} is still debated, it is possible that it shares mechanical modulation with its sarcolemmal counterpart (discussed in section “Ligand-activated MMC”).

The nuclear envelope shows significant deformation during application of mechanical forces to a cell.^{111–113} Nuclear mechano-sensing is an under-appreciated research area with significant importance for the understanding of mechanically induced changes in cell behaviour.¹¹⁴ In terms of ion channels, TRPV4 (Transient Receptor Potential Vanilloid 4) was localised in cultured neonatal rat ventricular myocytes in the nucleus only,¹¹⁵ though functional data confirming actual ion channel activity of this protein are still outstanding.

Of course, for MEF to affect heart rhythm, trans-membrane potential changes must occur, and the focus on sarcolemmal MGC is therefore not merely a consequence of conceptual restrictions or technical constraints (in terms of channel accessibility by recording tools), but related to the focus on functional responses of interest and, thus, the topic of this review.

Beyond Cardiomyocytes—Another potentially questionable preconception is that the normal heart consists chiefly of cardiomyocytes. While true in terms of volume fraction, non-myocytes such as endothelial and interstitial cells outnumber muscle cells in the heart. Endothelial cells of the cardiovascular system possess MGC,^{116–118} and so do

fibroblasts.^{119–121} While presumably required for functions such as shear sensing and directional extracellular matrix protein deposition in response to mechanical clues,¹²² ion channels in non-myocytes may affect cardiac electrophysiology *in the presence of heterotypic cell coupling* in the heart. Such coupling appears to exist in native myocardium, both in normal^{123–125} and fibrotic/scarred tissue,^{126, 127} as reviewed in detail elsewhere.¹²⁸

2. Cardiac SAC: Molecular Candidates

Criteria and Terminology

Knowledge about molecular candidates for cardiac MGC has seen significant improvements over the past decade. Candidate proteins and protein families have emerged, and new, often complex regulatory contributions have been proposed. At the same time, specific information about mechano-transduction pathways remains relatively limited. To address present controversies, Johanna Arnadottir and Martin Chalfie¹²⁹ suggested four criteria to establish whether or not a protein forms an ion channel that transduces mechanical forces and is relevant for organ function. 1: the protein must be expressed and localised in the mechanosensory organ. 2: the channel is required for mechano-sensitive responses, but not merely for normal development of the mechano-receptor cell or signalling downstream of the stimulus. 3: alteration of channel properties (conductance, kinetics, sensitivity, selectivity) alter the properties of mechanical responses. 4: the channel should be gated mechanically in heterologous expression system. In the mammalian heart, proteins have not generally been assessed as yet for these four criteria, highlighting avenues for further investigation.

In this review, SAC are sub-divided by their ion selectivity into K⁺-selective (SAC_K) and cation non-selective channels (SAC_{NS}).

SAC_K

Donghee Kim *et al.* described first whole-cell SAC_K currents (I_{SAC,K}) in cardiac cells.³² SAC_K are outwardly rectifying, allowing potassium ions to move more easily out of the cell than into it. They have large single channel conductances and inactivate in a time-dependent manner. Their activation causes membrane re- or hyperpolarization.⁶⁴ Single-channel recordings of I_{SAC,K} in adult mammalian cardiac myocytes have been obtained from atrial³² and ventricular myocytes.^{33, 130, 131} I_{SAC,K} is thought to be carried by K_{2P} (K⁺, two P-domain)* channels expressed in the mammalian heart.¹³² The most studied among them is TREK-1.

TREK-1 is active over a range of physiological membrane voltages. Channel gating is polymodal, activated by an impressive number of stimuli including intra- and extracellular pH, temperature, fatty acids, anaesthetics and, crucially, membrane deformation (curvature) or stretch.¹³³

*K⁺ channels with two P domains. A P domain is a short amino acid segment between two transmembrane helices that contributes to formation of the inner part of the pore, acting as a selectivity filter.

TREK-1 expression appears distinctly heterogeneous in the heart, with a gradient of mRNA expression that increases transmurally, from sub-epicardial to sub-endocardial myocytes.^{134, 135} This heterogeneity appears to correlate with transmural changes in MEF sensitivity, whereas stretch causes the most pronounced AP shortening in the sub-endocardium.^{136, 137} However, while TREK-1 mRNA expression was observed in murine atria and ventricles,^{132, 134, 138, 139} it has not, to our knowledge, been found in the human heart.^{140, 141} That said, whole-tissue mRNA, and even protein assays, are not necessarily true reflections of presence, let alone relevance, of a target, which may derive importance from high expression in a minority cell population (cardiac Purkinje fibres would be an example).

Where observed, TREK-1 protein appears to be arranged in longitudinal stripes on the surface of cardiomyocytes: a pattern that could support directional stretch sensing.¹³¹ Whole cell currents exhibiting the characteristics of recombinant TREK-1 (including sensitivity to volatile anaesthetics, arachidonic acid, pH, internal acidification, and stretch) have been observed in atrial and ventricular myocytes of several species including rat, mouse and pig.^{137, 142}

In terms of functional relevance, TREK-1 contributes to the 'leak' potassium conductance in cardiomyocytes.^{137, 143} As such, it aids normal repolarization and diastolic stability. However, increased TREK-1 current, for example during stretch, could shorten APD to a degree where this becomes pro-arrhythmic.¹³⁶ In keeping with this, several well-established anti-arrhythmic drugs, including lidocaine, mexiletine, propafenone, carvedilol, dronedarone, and vernakalant, inhibit TREK-1.¹⁴²

TREK-2 shares functional similarity with TREK-1, though little is known about its functional relevance in the heart. It appears active in chicken embryonic atrial myocytes,¹⁴⁴ and it is expressed in rat atria.¹³²

TRAAK is a TREK-1 homologue with similar biophysical properties and regulation,¹⁴⁵ expressed in the human heart.^{132, 146} TRAAK might form a human TREK-1 homologue, but its specific functional relevance in the heart is not yet known.

The similarity of electrophysiological properties of TREK-1, TREK-2 and TRAAK, and the overwhelmingly high expression levels of TREK-1 in murine model systems, may explain the paucity of experimental data on TREK-2 and TRAAK function. It is possible to differentially study them, as volatile anaesthetics activate TREK-1 and -2, but not TRAAK,¹⁴⁷ while extracellular acidification inhibits TREK-1 but activates TREK-2.¹⁴⁸ Detailed characterisation of the functional relevance of these MGC in mammalian heart in general, and in human tissue in particular, is a pre-requirement for consideration of their patho-physiological relevance and therapeutic target potential. This has, by and large, yet to occur.

BK channel activation is polymodal for a range of gating stimuli, which has given rise to different names for the same type of ion channel in a variety of studies (e.g. SAK_{CA}, BK_{Ca} Alpha, SLO1, MaxiK).¹⁴⁹ They are present in a number of cell and tissue types, including vascular smooth muscle, atrium and ventricles.¹⁵⁰ BK channels are found not only in the

sarcolemma, but also in membranes of the endoplasmic reticulum, the Golgi apparatus, and mitochondria.¹⁴⁹

Mechano-sensitivity of BK channels was established in membrane patches excised from cultured embryonic chick ventricular myocytes.¹⁵¹ However, as BK channels are activated by voltage changes *and* by alterations in intracellular Ca^{2+} concentration,¹⁵⁰ it has been suggested that their mechano-sensitivity is indirect, occurring secondary to stretch-induced changes in intracellular Ca^{2+} concentration.¹⁵²

As implied by their name, BK channels have large conductances. They have been suggested to contribute to heart rate control¹⁵³ and to offer cardioprotection during ischaemia.¹⁵⁴ Genetic variants of BK have been related with increased severity of systolic and general hypertension, as well as increased risk of myocardial infarction.¹⁵⁵

SAC_{NS}

Following on from the discovery of Sachs *et al.* of stretch-activated ion currents in avian skeletal muscle,²⁹ Craelius *et al.* identified SAC whole-cell currents in mammalian heart muscle. This current had the typical linear current-voltage relationship of weakly-selective ion channels, which we now attribute to SAC_{NS} ($I_{\text{SAC,NS}}$).³⁰ In contrast to SAC_K, SAC_{NS} have smaller conductances and a reversal potential closer to zero mV. With the reversal potential being positive to the resting potential of working cardiomyocytes, activation of SAC_{NS} will depolarise resting heart muscle cells, potentially triggering premature or ectopic excitation.⁶⁴

In contrast to SAC_K, no SAC_{NS} single-channel recordings have been obtained from freshly-isolated adult ventricular cardiomyocytes. This has led to the suggestion that SAC_{NS} may be hidden from patch pipette access, in membrane regions such as T-tub,¹⁵⁶ caveolae, or at intercalated discs.¹⁵⁷ A recent report suggests that $\alpha 1\text{A}$ adrenergic-agonists may cause translocation of a putative SAC_{NS} (TRPC6) from T-tub to the sarcolemma.¹⁵⁸ Whether this occurs physiologically, and the extent to which this might serve as a useful experimental intervention to facilitate single-channel recordings of TRPC6 in adult ventricular myocytes, remains to be explored.

The main molecular candidates for SAC_{NS} are Piezo and TRP channels.

Piezo1 and 2—The discovery of Piezo1 and Piezo2 by Ardem Patapoutian's group in 2010 represents a breakthrough in the field of mechano-transduction.⁴⁰ Piezo proteins form true SAC, meeting the four criteria listed above. Stretch-activation was demonstrated by heterologous expression of Piezo1 in HEK cells, which induced robust $I_{\text{SAC,NS}}$. Purified Piezo1, reconstituted into asymmetric bilayers and liposomes, forms ruthenium-red (a well-established pore blocker) sensitive ion channels, demonstrating that Piezo1 proteins are a pore-forming subunit of the channel.¹⁵⁹ Further investigation is required to clarify whether Piezo1 ion channel subunits are intrinsically mechano-sensitive.

Currently, no functional data have been published on Piezo1 or Piezo 2 in the heart. However, as Piezo channel properties are similar to those of endogenous cardiac SAC_{NS},

including (weak) voltage dependency, single channel conductance, inactivation, and sensitivity to GsMTx-4 (*Grammostola spatulata* Mechano-Toxin 4),¹⁶⁰ it is tempting to think that Piezo contributes to cardiac MEF.¹⁶¹

In terms of mRNA expression, Piezo1 has been observed in murine heart,⁴⁰ albeit at low levels in comparison to expression in lung, bladder or skin. However, mRNA or protein expression in tissue should be interpreted with caution. The two do not necessarily correlate to one another,¹⁶² and even if protein expression is confirmed, it does not necessarily prove the presence of functional ion channels. *Vice versa*, low expression levels do not rule out functional relevance of a protein, in particular if it is present in a minority cell population (such as Purkinje fibres, whose mechano-sensitivity was subject of the paper that coined the term ‘cardiac MEF’).¹⁰

This is an exciting and area of dynamic development. Basic science questions concerning structure, protein partners, and regulation of Piezo channels need to be addressed, as does the question of whether they are present in, and relevant for, the human heart.

TRP CHANNELS—Most mammalian TRP channels act as nonselective cation channels, passing Na⁺, K⁺, and in some cases Ca²⁺. They are widely expressed, involved in a variety of cell functions, and characterised by polymodal regulation.¹⁶³ While the presence and extent of direct stretch activation of these channels has remained controversial, results from heterologous expression systems suggest that some TRP are good SAC_{NS} candidates.

TRPC6 stretch-activation was characterised in HEK cells¹⁶⁴ but was not confirmed in CHO and COS cells.⁸² It has been suggested that TRPC6 require the angiotensin II type 1 receptor to be mechano-sensitive.^{163, 165} TRPC6 is among a small number of SAC candidates that are highly expressed in human heart homogenates.¹⁶⁶ In mouse heart, TRPC6 appears localised in T-tub and, in agreement with this observation, de-tubulation inhibits I_{SAC,NS} in murine ventricular cardiomyocytes.⁴⁹ Whole-cell patch clamp experiments on mouse cardiomyocytes identified robust I_{SAC,NS} in response to shear stimuli, which was inhibited by pore-blocking TRPC6 antibodies.⁴⁹ Murine TRPC6 knockout models suggest that the channel contributes to the slow force response, and may be involved in Duchenne muscular dystrophy,¹⁶⁷ highlighting the potential clinical relevance of TRPC6 manipulation. In non-myocytes, TRPC6 is proposed to promote myofibroblast transdifferentiation and it could act as a positive regulator in wound healing.¹⁶⁸ Putative roles, both in myocytes and non-myocytes, make this channel an interesting target for therapeutic intervention.

TRPC1 mechano-sensitivity is also discussed controversially. Stretch-activation of TRPC1 was first shown in *Xenopus* oocytes,¹⁶⁹ but has not been confirmed in other expression systems.⁸² Like TRPC6, this channel is likely to require the presence of a partner protein. Caveolin1 has been reported to be a trafficking regulator of TRPC1.^{170, 171} As caveolae are highly dynamic membrane regions, whose sarcolemmal integration is dynamically modulated by acute and sustained stretch,^{172, 173} this observation points to the possibility that TRPC1 is mechano-modulated but not mechano-gated.

TRPC3 protein has been identified in rat ventricular myocytes, where it is located in T-tubules.¹⁷⁴ In mouse neonatal cardiomyocytes, this channel is involved in ROS (Reactive Oxygen Species) production in response to mechanical stimulation or to perfusion of OAG (1-oleoyl-2-acetyl-sn-glycerol), a non-specific activator of MGC.¹⁷⁴ Recently, TRPC3/4 and 6 channels have been shown to contribute to pathological structural and functional remodelling after myocardial infarction.¹⁷⁵ Blocking these channels is suggested to reduce pathological remodelling and to improve contractility, making TRPC channels new therapeutic targets in the context of post-myocardial infarction.

TRPV2 is expressed in mouse heart^{157, 176} and has been reported to be activated by both cell-volume changes and patch pipette suction.¹⁷⁷ Using the TRPV2 agonist probenicid in wild-type and TRPV2 constitutive knockout mice, it was proposed that this channel contributes to baseline function of the cardiac calcium-handling machinery.¹⁷⁶ Like TRPC6, TRPV2 combines this putative physiological role with potential contributions to dystrophic cardiomyopathies in pathological settings. TRPV2 is overexpressed in dystrophic cardiomyocytes and contributes to Ca^{2+} influx. Interestingly, in cardiomyocytes challenged by osmotic shock, TRPV2 trafficking is impaired, leading to an accumulation of the protein on the sarcolemma and along T-tub, instead of their normal preferred location in the membranes of internal Ca^{2+} stores.¹⁷⁸

TRPM4 (Melastatin TRP channel 4) is expressed in cardiomyocytes of several species including mouse, rat, and human.¹⁶⁵ It has been implicated in stretch-activated responses of vascular smooth muscle.¹⁷⁹ Overexpression of TRPM4 may be involved in an inheritable form of progressive familial heart block type I,⁶⁷ though perhaps via mechanisms not directly related to TRPM4 mechano-sensitivity. Its physiological role in the heart is currently unknown.

TRPP2 (Polycystin TRP channel) is primarily found on the endoplasmic/sarcoplasmic reticulum and in primary cilia.¹⁸⁰ However, a TRPP2-like protein appears to function as a channel in the plasma membrane of rat ventricular cardiomyocytes,¹⁸¹ acting as a modulator of the cardiac ryanodine receptor, RyR2.¹⁸² Given its contribution to intracellular calcium cycling, TRPV2 dysregulation has been suggested to be involved in the development of heart failure.¹⁸³

3. Pharmacological Modulators

The best-known pharmacological tools to alter SAC activity are blockers of limited specificity, including gadolinium ions, amiloride, and cationic antibiotics (streptomycin, penicillin, kanamycin). Caution is needed, in this context, when interpreting research on stretch-effects in cultured cells, as standard media contain antibiotics that may alter (reduce) background availability of SAC.

In spite of their limited selectivity, the above SAC-blockers have been highly productive for experimental cell research, as reviewed elsewhere.^{93, 184} Their utility in whole animal or human studies is limited though. Thus, gadolinium is chelated almost completely in solutions that contain physiological pH-buffer systems,¹⁸⁵ while clinically used compounds (amiloride, antibiotics) exert their effect primarily and predominantly *via* their established

pharmacological targets, rather than possible (side-)effects on SAC. Also, not always is *in vitro* behaviour indicative of *in situ* response patterns. Thus, streptomycin's ability to block stretch-responses in isolated cells¹⁸⁵ is not necessarily preserved over the same concentration ranges and response times in native tissue,¹⁸⁶ highlighting the possibility of false-negative findings on SAC-contributions probed using the antibiotic in more integrative model systems.

A number of other clinically-applied compounds affect molecular SAC candidates with a relatively narrow spectrum of action. TREK-1 activity, for example, is modulated by the neuroprotective agent riluzole (10–100 μ M), the antidepressant fluoxetine (Prozac; IC₅₀ ~10 μ M), and millimolar concentrations of volatile halogenated and gaseous general anesthetics,¹⁴⁵ in the case of channel activation with the potential for unexpected false-positive effects in studies on anaesthetised mammals.

Among the few specific SAC inhibitors identified is the peptide GsMTx-4,¹⁶⁰ isolated by Sachs *et al.* from a Chilean tarantula venom.¹⁸⁷ In contrast to SAC_K, SAC_{NS} are distinctly sensitive to this peptide, though the mechanism of this specificity is unknown. GsMTx-4 inhibits TRPC5,^{73, 188} TRPC6,^{164, 189} and Piezo1 channels, when applied to the external membrane.^{190, 191} Both the D and L enantiomers of GsMTx-4 block SAC_{NS}, showing that the mechanism of action is not stereospecific or chiral.¹⁹² Instead, the mode of action of GsMTx-4 is thought to involve insertion into the outer membrane leaflet (GsMTx-4 is an amphipath) in the proximity of the channel, relieving lipid stress sensed by the channel and favouring the closed state of SAC.¹⁹² Counterintuitively, GsMTx-4 sensitizes bacterial MscS and MscL to increased tension,¹⁹³ while it has no effect on TREK-1.¹⁹⁰ The mode of action of GsMTx-4 on SAC requires further elucidation.

A SAC_K specific blocker is Spadin. It inhibits TREK-1 mechano-gating,¹⁹⁴ without affecting TREK-2 and TRAAK.¹⁹⁴ Additional TREK-1 modulators, including activators, have recently been identified by Sviatoslav Bagriantsev *et al.*,¹⁹⁵ and the utility of these compounds for cardiac MEF research awaits exploration. Cardiac potassium-selective MMC that have been probed using specific inhibitors include K_{ATP} channels. The mitochondrial K_{ATP} is inhibited by the 5-hydroxydecanoate (5-HD), while HMR-1098 has been identified as an antagonist for the sarcolemmal K_{ATP}.^{110, 196} Glibenclamide is also a popular pharmacological tool, inhibiting sarcolemmal K_{ATP} from either side of the membrane.¹⁹⁷

Concerning TRP channels, TRPC6 antibodies have been used as specific inhibitors of stretch-responses in isolated cells.⁴⁹ More generally, TRPC6 is modulated by hyperforin,¹⁹⁸ TRPV1 by capsaicin,¹⁹⁹ TRPV2 by probenidol,²⁰⁰ and TRPM4 by 9-phenanthrol.²⁰¹

If specific inhibitors are rare, even fewer specific activators have been identified. Recently, Yoda1 has been shown to be an agonist for both human and mouse Piezo1, affecting sensitivity and inactivation kinetics of the channel. This compound does not act via protein partners of the channel as it is still efficient in artificial bilayers.²⁰² If confirmed in native heart tissue, it would represent a powerful tool to investigate Piezo1 functions in integrated systems, especially if the channel was closed in physiological conditions.

The potential for MGC and MMC modulators as pharmacological tools in heart rhythm management has been expertly reviewed by Ed White.¹⁰⁶ Considering the ubiquitous presence of these channels in all cell types of the human body, pharmacological interventions targeting a specific organ are challenging, requiring selective delivery and avoidance of side-effects on other body functions. A possibility here is genetic targeting, with the potential of not only aiming for a specific organ, but for a specific cell type in that organ (cardiomyocytes, endothelial, interstitial or immune cells, etc.) or a defined disease progression stage. Again, this is a domain of research requiring additional effort/focus.

4. Mechanistic Projection Between Levels of Investigation

The heart generates, experiences, and responds to a highly dynamic mechanical environment. Parameters relevant for cardiac mechano-reception change dynamically and on a range of different time scales, from years (e.g. ontogenesis, disease development, or aging) to fluctuations that are circadian (e.g. physical activity), spread over tens of seconds (e.g. respiratory cycle induced alternations in venous return), or happen in milliseconds (e.g. mechanical activation during a heartbeat). MGC are, jointly with photo-transduction systems, among the most rapid sensors in biological systems, though they may make contributions over the whole range of time scales mentioned above.

Knowledge about SAC-contributions to chronic cardiac conditions is limited, although they have been implicated in the development of cardiac hypertrophy and heart failure.^{203–205} Identification of causal chains of events is difficult in chronic disease, as a host of relevant parameters, from tissue and cell visco-elastic properties to ion channel expression,²⁰⁶ remodel.

Projection from SAC activity to cell and tissue levels during acute stretch-induced changes in cardiac electrophysiology is more straightforward. Activation of SAC_K , with their reversal potential negative to the resting membrane potential of cardiac cells, will tend to hyperpolarize resting cells. SAC_{NS} , in contrast, with reversal potentials typically between 0 and -20 mV in cardiac cells, will in turn depolarize resting cells, if sufficient current flow is generated.²⁰⁷ Interestingly, all stretch-induced changes in resting membrane potential of cardiac myocytes reported so far involved depolarization, up to and including mechanical induction of AP.¹⁵ Resting membrane depolarization can be explained by SAC_{NS} , but not by SAC_K , suggesting that the latter do not normally determine acute electrophysiological response patterns of the heart to diastolic mechanical stimulation.

Matters get more complicated during the AP, when timing of mechanical stimuli warrants closer examination. While SAC_K activation would continue to have a re- or hyperpolarizing effect, SAC_{NS} will do so only while membrane potential levels are positive to the SAC_{NS} reversal potential. As a consequence, SAC_{NS} activation will shorten APD during early repolarization but may, if sustained or applied late in the AP, give rise to late AP prolongation, or even after-depolarization-like events (Figure 3). Indeed, both early and late stretch-induced after-depolarization-like behaviour have been reported in cardiac research.⁶⁴ If supra-threshold, these may mechanically trigger ectopic excitation.²⁰⁸

Timing-dependence of stretch effects on cellular electrophysiology matters also for the projection from cell to organ/organism levels, as both electrical activation and repolarization are characterised by a wave-like behaviour across the heart. This means that the ECG offers an inherently limited temporal reference for characterization of local events, as illustrated in more detail in section 5.

Quantitative projection from molecule to organism, including elucidation of spatio-temporal modulators of stretch responses, has benefitted from computational modelling.^{209–211} Interestingly, the vast majority of observed acute electrophysiological responses of the heart to stretch can be successfully reproduced simply by invoking SAC_{NS}.²¹²

Of course, computational demonstration of quantitative plausibility is neither proof nor replacement of experimental validation. Occasionally, such validation trails computational predictions by a decade or more. An example are models of impact-induced arrhythmogenesis (aka *Commotio cordis* [CC], agitation of the heart, without structural damage),^{3, 4} which – using 2D²¹³ and 3D²¹⁴ simulations – concluded that the rare but devastating CC-induced ventricular fibrillation (VF) requires spatio-temporal overlap of mechanically-affected tissue with the trailing edge of the repolarization wave. This has now been confirmed experimentally (see also section 5).²¹⁵

Among the present challenges in projecting from protein to pathology is the difficulty of assessing and comparing actual effective mechanical parameters of ion channel stimulation. Few studies have quantified the stretch imparted upon patch-clamped membranes during SAC investigations.²¹⁶ At the cell and tissue level, cell or sarcomere length (SL) are used as a read-out of strain,²¹⁷ and occasionally as an input parameter to gauge mechanical modulation of cardiomyocytes.^{24, 218} In native heart, implanted ultrasonic transducers,²¹⁹ echo and MRI²²⁰ have all been applied to characterise transmural deformation patterns. But, and this is a crucial limitation: none of these techniques allows one to actually measure stress/force inside the preparation (whether a membrane patch, a cell, or a tissue/organ). An exciting development here is the advent of fluorescent force reporters,²²¹ whose application to cardiac MEF research could revolutionise concepts and understanding of cardiac mechano-sensitivity.

5. Clinical Relevance

In terms of physiological beat-by-beat effects, activation of SAC has been shown to underlie the non-neural component of the stretch-induced increase in spontaneous sino-atrial node (SAN) cell pacemaking rate, aka the Bainbridge effect.²⁰ Block of SAC using GsMTx-4 (but not using streptomycin, see section 3) terminates this positive chronotropic response in native SAN tissue explants¹⁸⁶ which, in its guise of a respiratory sinus arrhythmia, persists at whole body level – even in heart transplant recipients and/or after additional pharmacological denervation.²²²

Surprisingly, this is about all we know *for sure* regarding the physiological relevance of SAC in heart rate and rhythm regulation.

It is possible, perhaps probable, that the key role of cardiac SAC under normal conditions is related to auto-regulation of contractile behaviour. This could occur via stretch-dependent adjustment of trans-sarcolemmal Ca^{2+} influx,²²³ preservation of intra-cellular Ca^{2+} secondary to stretch-induced trans-sarcolemmal influx of Na^+ ,^{152, 224} and/or stretch-modulated grading of Ca^{2+} release from the SR.²¹ Any or all of these mechanisms could contribute to both acute (Frank-Starling response)²²⁵ and sustained (slow force response)²²⁶ adjustments of cardiac contractility to changes in the heart's mechanical environment (highly relevant for contractile cells in the heart, given that they are *not* controlled via neuro-muscular junctions, such as is the case in skeletal muscle), while their effects on cardiac electrophysiology would be 'secondary'.

In contrast, SAC have been implicated in a host of clinically relevant scenarios, from acute arrhythmogenesis, to sustenance and termination of arrhythmias, as explored next.

Mechanical Induction of Arrhythmias (Acute)

As mentioned before, stretch of resting myocardium, if strong enough to cause any change in membrane potential, gives rise to depolarization, potentially triggering ectopic excitation. In human volunteers, this has been shown to occur upon external mechanical energy delivery such as by precordial tapping, at energy levels as low as 0.04 J (equivalent to dropping a golf ball [46 g] from a height of 9 cm).^{227, 228} Mechanically-induced ectopy is a common adjunct to intra-cardiac device-tissue interactions such as during cardiac catheterization,²²⁹ and it may even be triggered by the heart's own mechanical activity, such as upon acute obstruction of ventricular outflow during balloon valvuloplasty.²³⁰

Mechanically-induced ectopy is usually benign, but in the context of pre-existing pathologies, it may give rise to sustained tachyarrhythmias. In a porcine model of pathologically prolonged QT-intervals, for example, β -adrenergic stimulation by bolus-injection of isoproterenol can give rise to ventricular after-contractions, originating from near-endocardial locations. These after-contractions precede early after-depolarization-like behaviour in near-epicardial tissue. Upon reaching threshold for induction of ectopic excitation, this can initiate *torsades de pointes*.²³¹

Much rarer than mechanically induced ectopy, but more widely known, is CC, in particular in its most severe form of CC-induced VF. Here, a mechanical impact to the precordium, usually by a projectile such as an ice hockey puck or baseball, gives rise to acute MEF responses that – during a very narrow critical window of about 20 ms – can cause instantaneous induction of VF.²³² The mechanisms underlying VF induction are discussed controversially, with focus either on abnormal repolarization²³³ or on abnormal excitation overlapping the trailing edge of normal repolarization.³ Also, the role of the impact-associated surge in intra-ventricular pressure is subject of debate, while it is accepted that local mechanically-induced ectopy occurs in myocardium nearest to the site of mechanical stimulation, both in isolated heart^{215, 234} and whole animal.²³⁴

Recent optical mapping studies of isolated heart models of CC have confirmed that SAC_{NS} are involved in the generation of ectopic excitation, and that deterioration into VF is seen only if ectopy occurs right on the edge of the preceding normal repolarization wave.²¹⁵ This

confirms prior modelling-based predictions²¹³ and sheds further light on the unusually narrow critical window for mechanical induction of VF in whole animal studies: the pre-condition for overlap of mechanical stimulus and trailing repolarization edge is met for any specific pre-cordial impact location for a brief part of the ECG cycle only (if one could mechanically stimulate other parts of the heart by extracorporeal impact, the accompanying critical time window would be shifted). Thus, the critical window for VF-induction during CC exists in time and in space, reconfirming that systemic (ECG) and local (AP) timings are not interchangeable.

Mechanical Sustenance of Arrhythmias (Chronic)

Mechanical contributions to chronic arrhythmias have been implicated in the perpetuation of both atrial^{235–237} and ventricular tachycardias.²³⁸ Mechanisms here may range from activation of SAC that alter APD,²³⁹ slow conduction velocity,^{173, 235, 238} or increase dispersion of repolarization,²³⁸ over changes in expression of mechanically modulated ion channels²⁰⁶ and alterations in connexin phosphorylation,²⁴⁰ through to remodelling of tissue architecture, composition,²⁴¹ and innervation.²⁴²

Given the multiplicity of mechanisms and pathways involved, and the variable time scales over which they manifest themselves, this area is understudied, in particular with regard to ventricular arrhythmogenesis. A conceptually interesting approach to probing effects of sustained ventricular stretch in cardiac arrhythmogenesis has been employed by Menashe Waxmann *et al.*,²⁴³ who used the *Valsalva manoeuvre* to temporarily reduce ventricular volume overload in tachycardiac patients, achieving spontaneous (it temporary) return to normal sinus rhythm. Since the intervention also works in heart transplant recipients,¹² the most probable explanation is that sustained stretch is pro-arrhythmogenic.

The demonstration of tachycardia termination by temporary reduction in ventricular load highlights that chronic mechanical effects on heart electrophysiology are a clinically relevant target for further research. A perhaps particularly important aspect is the border zone of local (post-)ischaemic foci²⁴⁴, where mechanically-promoted arrhythmogenesis²⁴⁵ has been prevented in whole animal studies by application of a mechanical constraint that curtails ischaemic segment lengthening during contraction of the surrounding healthy myocardium.²⁴⁶ The same intervention delayed extracellular potassium accumulation, suggesting mechanical modulation of trans-membrane ion fluxes, perhaps involving sarcolemmal K_{ATP} channels.

Mechanical Termination of Arrhythmias

Beyond removal of sustained overload, acute mechanical interventions, such as by precordial thump ('fist-aid'), have been known for at least a century to be of therapeutic potential.²⁴⁷ It is assumed that the short sharp impact to the chest is transmitted to the heart, where – presumably via activation of SAC_{NS} – it triggers ectopic activation in excitable tissue.²⁴⁸ Such activation can be used to pace the quiescent heart, or to obliterate excitable gaps in hearts containing re-entrant activation waves.

The latter scenario is less straightforward, given that excitable gaps, in particular in the presence of multiple re-entry pathways, are unlikely to be accessible from the limited extent of precordial impact locations. In addition, in conditions of severe pre-existing ischaemia, the depolarizing effect of SAC_{NS} activation may be off-set, in part, by ischaemic and mechanical co-activation of K_{ATP} channels,⁵⁸ potentially rendering mechanically-induced depolarization less effective.²²⁹ Accordingly, early hopes, based predominantly on (publication-bias prone) case reports²⁴⁹ for thump-version of tachyarrhythmias, have not been sustained in more recent prospective human study designs.^{250–253} Accordingly, precordial thump application has been discouraged in recent ILCOR statements.²⁵⁴

Precordial thump-pacing in bradycardia or primary asystole, however, remains a potentially productive intervention,^{255, 256} for example to bridge between witnessed asystolic arrest and application of electrical device-based rhythm management.²⁵⁷ As evident from the 2010 ILCOR statement, precordial thump in asystole warrants further investigation, taking us full circle to the original 1920 paper by Eduard Schott, who kept Stokes-Adams Syndrome patients during episodes of intermittent atrio-ventricular conduction block conscious for extended periods of time by mechanical fist-pacing only.²⁴⁷

6. Outlook

By and large, acute electrophysiological responses of the heart to mechanical stimulation can be explained, qualitatively and quantitatively, through activation of SAC. This in itself does not prove that they are sole or main drivers of responses. But, given the ability of increasingly selective pharmacological tools to probe responses in model systems from patch to patient, it seems reasonable to consider these ion channels as clinically relevant targets for management or correction of cardiac electrical activity.

So – what are the main challenges?

At the basic science end, the perhaps most important question relates to the mechanism(s) of activation of MGC. Mechanical stimuli span all scales from nano to macro (an overview of the sizes of main mechano-sensitive structures and proteins can be found in Figure 4). Their quantification in living systems is particularly challenging at cellular and sub-cellular levels.

It is known from *in vitro* experiments that sarcolemmal in-plane tension, curvature and thickness, lipid composition affect MGC activity. In addition, the cytoskeleton can gate MGC. Non-sarcolemmal responses, such as the stretch-induced increase in calcium spark rate for example, require the integrity, here of microtubules.²¹ Sarcolemmal TREK channels are inhibited by actin,¹⁴³ while Piezo1 channels need the actin cytoskeleton to fully activate.²⁵⁸ In addition Piezo1 can be inhibited by the cytoskeleton-protein cross-linker filamin A in smooth muscle.²⁵⁹ Thus, the cytoskeleton may, both, cause MGC activation or protect them from opening. An additional layer of complexity arises from the fact that cytoskeletal integrity affects membrane tension and shape of the cell and its organelles.²⁶⁰ This may provide a further, potentially indirect, path to affecting MGC gating. Thus, even though MGC were discovered more than 30 years ago, the actual biophysics of channel activation *in vivo* has remained elusive.²⁶¹

That said, membrane ‘stretch’ is usually taken to be the obvious driver of MGC activation, but what are the relevant properties and descriptors of such stretch? Existence and extent of in-plan tension in membranes of cardiac cells is not known. What is known is that lipid bilayers are not distensible (strain exceeding 2–3% of ‘slack area’ causes membrane failure),^{262–264} so reservoirs (membrane invaginations, vesicles, caveolae)^{172, 173, 265} are known to buffer membrane tension variations *via* quick (<100 ms)²⁶⁶ membrane surface adaptation.²⁶⁷ Thus, in-plan membrane tension may not increase linearly with stretch, rising more prominently when some of the membrane reserves have been extinguished.²⁶⁸ This condition may be present *in vitro* more frequently than *in vivo*, as cells swell upon isolation, ‘losing’ structurally identifiable caveolae, and hence potentially biasing experimental observations. This could include either heightened mechano-responsiveness, or reduce differential stretch effects, as a result of pre-activation of certain mechano-sensitive pathways.

Related to tension (via the law of Laplace), but presumed to be an independent activator of MGC, membrane curvature is present both in the plasma- and in endo-membranes. Effective strains are related to size and shape of mechano-sensitive structures, and it is thought that curvatures only with radii in the range of ion channel dimensions (i.e. few nanometers)²⁶⁹ will act as directly relevant signals. While optical monitoring of membrane curvature in live samples (membrane patches, cells) is possible, this tracks larger radii only. A real understanding, therefore, of the biophysics involved in translating a macroscopic mechanical stimulus into a microscopic event, capable of increasing the open probability of an ion channel, is one of the key missing ingredients in developing a mechanistic understanding of mechano-electric coupling.

Thankfully, techniques are emerging that will allow quantification of mechanical properties experienced by individual cells in the tissue.

FRET (Förster Resonance Energy Transfer)-based tension probes have started to be used to assess dynamic changes in cytoskeletal tension, thus far in non-cardiac cells. This measuring approach is based on the energy transfer between two chromophores whose distance changes as a function of the mechanical environment. As the efficacy of energy transfer (which is measured as a shift in emitted fluorescence) is inversely proportional to this distance with a power of 10^6 , FRET probes are highly sensitive to minute changes in strain, and they can be used *in vivo* to characterise cytoskeletal tension in real time.^{221, 277, 278} A conceptually similar approach is being taken towards assessment membrane mechanical properties in native cells. Using a FRET tension probe, inserted into a mechano-sensitive protein, it has been possible to track conformational changes at the ion channel level in living cells.²⁷⁹ Constructs like this could be used as tension reporters for various lipid bilayers, including non-sarcolemmal membranes.

At the applied end, one of the key challenges is to identify the molecular nature of individual ion channels involved in electrophysiological responses of the human heart to changes in the mechanical environment. Building on that, intervention tools that are organ-, or better cell- and/or disease-state specific, may hold a key to novel therapeutic opportunities.

A more long-term aim will be to decipher the complex pathways of mechanically induced changes in cell and tissue structure and function, which contribute to chronic responses to mechanical overload. Given that we are still unsure whether stress or strain are ‘the’ key activators of MGC, it is difficult to decipher response patterns driven by volume- and pressure-challenges (or by pre- and afterload) in the whole organ.

The most complex setting – chronic overload combined with acute stretch (such as may occur in ischaemic border zone tissue, for example) – is perhaps the clinically most relevant immediate target, as focal excitation occurs acutely, and in relation to local stretch maxima. An MGC modulator that would be metabolic state-specific (e.g. perhaps pH-dependent) could potentially be applied systemically, yet act where needed. This is an area deserving targeted study.

Another challenge lies in the multiplicity of non-channel structures that are mechano-sensitive,²⁸⁰ making an understanding of the roles of mechanical forces more complex.

Caveolae are known to act as membrane reserves that can buffer variation of membrane tension. They were shown to limit VAC ($I_{Cl,swell}$) activation in rat ventricular myocytes,²⁶⁷ and are implied as the substrate for stretch-induced conduction slowing (acting via mechanical unfolding, increasing effective surface membrane area).¹⁷³

Also, Caveolin3 (Cav3) can modify integrin function and mechano-transduction in cardiomyocytes and intact heart,²⁸¹ while Cav1 in endothelial cells of murine coronary arteries is a critical requirement for shear stress-mediated vasodilatation.²⁸² Caveolins are also tightly linked to some TRP-channels, making caveolae another most interesting component of mechanical transduction pathways, including those relevant for MEF.

Last, but not least, T-tub – sarcolemmal membrane invaginations that dive deep into the centre of cardiac myocytes – contain MGC (TRPC6) and MMC (Kir2.3).⁴⁹ They deform rhythmically on a beat-by-beat basis^{172, 283} and may be one of the more under-estimated physiologically-relevant mechano-transducers in the heart. For a more extensive overview of non-channel structures involved in mechano-transduction processes we refer to Hirata *et al.*²⁸⁰

7. Conclusion

MGC in the heart affect cardiac electrophysiology. While mechanical activation of ion transport pathways may be an evolutionary inheritance of the need, even for the earliest cells, to respond to osmotic challenges, SAC in (osmotically more stable) multicellular systems may have conferred other advantages. For muscle cells, this may include the adjustment of contractility to local mechanical demand. The fact that MGC carry ion currents that can affect heart rate and rhythm may, thus, be a ‘side effect’. But, even if so, it is one that matters for maintenance of normal heart rate and for the induction or termination of heart rhythm disturbances. Any therapeutic targeting will need to involve a three-pronged approach, that considers potential electrophysiological benefits in the context of the need to maintain volume regulatory capacity (say in ischaemia, and even more so, reperfusion) and the ability to tune cell contractility to the mechanical environment. In fact, the latter is

particularly important for the heart as, in contrast to skeletal muscle, individual myocytes must ‘match’ their mechanical performance to that of their neighbours in the absence of neuro-muscular junctions or other cell-external mechanisms to grade contractile activity. What is clear, though, is that any concept of cardiac electro-mechanical activity that ignores the information flow from mechanics to electrics is unnecessarily limited – and outdated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Nonstandard Abbreviations and Acronyms

AChR	AcetylCholine Receptor
AP	Action Potential
APD	Action Potential Duration
ASIC	Acid-Sensing Ion Channel
BK	Big K⁺ channels
CaT	Calcium Transient
Ca_v	Calcium channels Voltage-gated
[Ca²⁺]_i	Calcium concentration, intracellular
CC	Commotio cordis
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CLC	Chloride Channels
GluN2B	GluRepsilon2/NR2B
K_{ATP}	K⁺ channel, ATP-inactivated
K_{2P}	K⁺ channels with 2 P domains
KCNQ	K⁺ Channel, voltage gated, KQT-like
Kir	K⁺ inwardly-rectifying channel
Kv	K⁺ channel Voltage-gated
KvAP	K⁺ channel Voltage-gated from <i>Aeropyrum pernix</i>
MCA	Mechano-sensitive Ca²⁺ channel
MEC	Mechanosensory abnormal

MGC	Mechano-Gated Channels
Mid1	Mating Induced Death
MscA	Mechanso-sensitive channel Archaeon
MscK, L, M, S	Mechanso-sensitive channel of K⁺, Large, Medium, Small conductance
MscMJ	Mechanso-sensitive channel of <i>Methanococcus jannashii</i>
MSC1	MscS homolog in <i>Chlamydomonas reinhardtii</i>
MSL	Mechanso-sensitive channel of Small conductance like
Na_v	Sodium selective channel Voltage-gated
NMDA	N-methyl-D-aspartate
NOMPC	No mechanoreceptor potential C
OSM	OSMotic avoidance abnormal family
ROS	Reactive Oxygen Species
RyR	Ryanodine Receptor
SAC	Stretch-Activated Channels
SAC_K	SAC, K⁺-selective
SAC_{NS}	SAC, cation non-selective
SL	Sarcomere length
SAN	Sino-Atrial Node
TASK-1	TWIK-related acid-sensitive K⁺ channel
TPK	Two-pore K⁺ channels
TRAAK	TWIK-related arachidonic acid-activated K⁺ channel
TREK	TWIK-related K⁺ channel
TRP	Transient Receptor Potential
TRPA, C, M, N, P, V, Y	Transient Receptor Potential Ankyrin, Canonical, Melastatin, NOMP, Polycystin, Vanilloid, Yeast
T-tub	Transverse tubule
TWIK	Tandem of two-pore K⁺ domains in a weak inwardly rectifying K⁺ channel
VAC	Cell Volume-Activated Channels
VF	Ventricular Fibrillation

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Figure 1. MGC and mechanically modulated channel (MMC) candidates are present throughout living organisms. Several mammalian channels have homologues in other organisms: e.g. NOMPC, OSM9, TRP4, TRPY1 and LOV-1 are TRP homologues; MEC channels are members of the DEG/ENaC superfamily whose mammalian representatives are ASIC channels; TPK is a homologue of K_{2p} channels; Mid1 is homologous to voltage-gated calcium channels. In red: channels expressed in the heart; underlined: channels clearly identified as MGC; channels with no known mammalian homologues are marked by *. “SAC_{NS}”: stretch-activated channels, cation non selective; “SAC_K”: stretch-activated channels, potassium selective; “Mito”: mitochondria; “SR”: sarcoplasmic reticulum. Only a selection of the more well-known channels and receptors is presented; protein names for mammals are explained in Section 2.

MMC		MGC		
Voltage	Ligand	SAC		VAC
KvATP	NMDA receptor	SAC _K	SAC _{NS}	TRPA1
Kv1.5		TREK-1, 2	Piezo1	TRPC1, 3, 6
Kir2.1, 2.2, 2.3	AChR	TRAAK	Piezo2	TRPV1, 2, 4
L-type	K _{ATP}	BK?		TRPM3, 4, 7
Nav1.4, 1.5, 1.6, 1.7				TRPP2
			Connexin46	ASIC

Figure 2.

Mechanically Modulated Channels (MMC) versus Mechanically Gated Channels (MGC). Presentation includes channels understood to be activated by transmembrane voltage, ligands, stretch (SAC: Stretch Activated Channel) or intracellular volume change (VAC: Volume Activated Channel). In red: channels expressed in the heart.

Figure 3.

Stretch greatly modifies the action potential (AP). Representative recordings showing the effect of stretch intensity on AP and resting membrane potential in single isolated cardiomyocytes. Stretch was applied during the entire duration of recordings, scaled to control cell length (left: moderate stretch, right: large stretch); control recordings: black; stretch: red. Red arrows indicate putative contributions of SAC_{NS} , blue arrows represent potential effects of SAC_K . Adapted from Kohl et al.³

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Figure 4. size matters. Strain is greatly influenced by size and shape of affected structures, and spans all scales from nano to macro. Tools to study mechano-sensors are listed on the left in parallel with milestones. Membrane (blue), cytoskeleton (red), measuring probes (green), others structures (black) are annotaed. MRI: Magnetic Resonance Imaging, AFM: Atomic Fore Microscopy, Ø: diameter.