22

Mechanical triggers and facilitators of ventricular tachy-arrhythmias

T. Alexander Quinn and Peter Kohl

Background

The heart can adjust its performance to acute changes in circulatory demand, even after transplantation, which illustrates that cardiac mechano-sensitivity is an efficient contributor to the (auto-)regulation of the heartbeat. Cardiac function involves multiple interdependent mechano-sensitive pathways, including those that feed information about the mechanical state of the myocardium to the electrical processes of excitation and conduction. This mechano-electric feedback forms part of the overall mechano-electric coupling (MEC) concept, which considers the heart as an integrated electro-mechanical organ. MEC can be observed at all levels of cardiac structural and functional integration, from (sub-)cellular and tissue levels, to whole organ and patients[1]. Perturbations of the heart's mechanical status can occur as a consequence of both intrinsic and extrinsic stimuli.

Intrinsic stimuli include changes in venous return that determine cardiac preload (e.g. Chapter 13), alterations in cardiac afterload (e.g. Chapter 37) and intracardiac stress-strain inhomogeneities that arise in normal (e.g. Chapter 21) and pathologically disturbed myocardium (e.g. Chapter 48) as a consequence of the heart's own contractile activity. The mechanisms underlying MEC are normally either 'electro-physiologically silent' or physiologically beneficial, so one should not regard MEC as arrhythmogenic *per se*. The preload-dependent modulation of cardiac Ca^{2+} handling, for example, that contributes to the Frank–Starling response of the heart is thought to act as an equalizer of cellular contractility, allowing individual cardiomyocytes to operate in mechanical balance with their neighbours. Classic Frank–Starling mechanisms allow instantaneous adaptation in contractile behaviour without changes in intracellular Ca^{2+} load. For adaptation to sustained changes in mechanical load, however, the trans-sarcolemmal Ca^{2+} flux balance must be affected. The electrophysiological consequences of mechanisms that support Na^+ and/or Ca^{2+} gain (such as stretch-activated channels, SAC) may be more apparent than SAC effects on ion balance. Therefore, mechano-electric phenomena may arise as 'side-effects' of mechanisms that support other physiological functions. This finds manifestation in pathological conditions involving inhomogeneous stress-strain distributions, where regional mechanical modulation of Ca^{2+} handling can give rise to arrhythmogenic Ca^{2+} waves (see Chapter 16).

Extrinsic (to the myocardium) stimuli may occur in the context of invasive medical interventions (such as cardiac catheterization) or as a consequence of extra-corporeal impacts (e.g. during *Commotio cordis*, or in the context of precordial thump application for cardioversion). As in the case of intrinsic mechanical stimuli, mechanical interventions are normally electrophysiologically silent (no effect) or benign (perhaps triggering an extra beat, without causing sustained arrhythmias). Nonetheless, as illustrated by the topic of this book, MEC has clear clinical relevance, and both initiation (see Chapters 31 and 45) and termination of arrhythmias by mechanical means (see Chapter 50) have been observed.

The present chapter explores the roles of mechanical factors in the genesis of ventricular tachy-arrhythmias. Conceptually, tachy-arrhythmogenesis is thought to be a consequence of the combined action of a *trigger* event and a *sustaining mechanism* (both may be 'merged', such as when repetitive generation of a trigger [focal activity] maintains tachy-arrhythmic activity). Ventricular tachy-arrhythmias are frequently encountered in pathologies associated with volume and pressure overload, such as in patients with valve disease, ischaemia, infarction, cardiomyopathy or heart failure (e.g. Chapter 56). This is caused, at least in part, by cellular electrophysiological responses to changes in myocardial strain[2]. However, in the setting of chronic diseases it is difficult to identify causal relationships, as cardiac MEC responses occur on the background of structure–function remodelling and in the presence of changes in metabolic state, autonomic control, and responsiveness to pharmaceutical interventions.

Consideration of acute effects of changes in the mechanical environment can help to elucidate these mechanisms, even in the chronic setting. For instance, *acute removal* of ventricular volume overload by the Valsalva manoeuvre has provided one of the most impressive illustrations of the arrhythmogenicity of sustained strain: with the reduction of ventricular dimensions (a consequence of blood redistribution caused by a change in thoracico-abdominal pressure gradients), ventricular tachycardia (VT) ceases in patients[3], even after surgical denervation of the heart (transplant recipients)[4].

More commonly, however, acute *application* of mechanical stimuli is investigated, often in the healthy heart, which somewhat restricts the applicability of observations to chronic disease states. Nonetheless, acute changes in myocardial strain, whether global (e.g. increased intraventricular volume) or regional (e.g. extrinsically applied local mechanical stimulation, or intrinsic paradoxical segment lengthening during local metabolic impairment), has been shown to have pronounced effects on cardiac electrophysiology. Experimental investigations in isolated whole heart, tissue, and cellular models have provided insight into the translation of mechanical factors into triggers (ectopic excitation of myocardial tissue) and facilitators (promoting re-entry) of ventricular tachy-arrhythmias.

Effects of acute mechanical stimulation on heart rhythm: temporal aspects

General considerations

One of the major mechanisms underlying MEC is activation of specialized, mechano-sensitive ion channels. These can be divided into SAC that increase their open probability in direct response to cell deformation and cell-volume activated channels (VAC) that respond, usually with some delay in cardiomyocytes, to an increase in cytosolic volume. Acute mechanical stimulation of the heart is assumed to not be associated with changes in cell volume (for information on VAC and their roles in settings such as ischaemia, reperfusion and hypertrophy, see Chapters 4 and 51).

Interestingly, most of the *acute* cardiac electrophysiological responses to mechanical stimulation can be explained by considering effects mediated via sarcolemmal SAC, although non-sarcolemmal SAC (Chapter 5), changes in cellular Ca^{2+} handling (Chapter 10), effects on other messenger systems (Chapter 11) or interaction with non-cardiomyocytes (Chapter 19) are undoubtedly important contributors to MEC. In addition, the open probability of many ion channels that are not customarily regarded as SAC is sensitive to the mechanical environment (see Chapter 6), highlighting the multitude of possible pathways underlying cardiac MEC.

Since the discovery of SAC in cardiac cells over two decades ago[5,6], their properties and contribution to arrhythmogenesis have been important targets of basic and applied research. Two categories of SAC can be distinguished, based on their ion selectivity: cation non-selective SAC (SAC_{NS}), with a reversal potential somewhere half-way between peak action potential (AP) and resting potential levels (usually around –20 to 0 mV), and K^+ selective SAC (SAC_K), with a reversal potential that is negative to cardiomyocyte resting potential (i.e. near the potassium equilibrium potential, usually between –90 and –95 mV)[7–9].

The reversal potential is an important determinant of acute SAC effects on cardiac myocytes as it acts like a sink-hole towards which, if opened, the cell's membrane potential will be drawn. Thus, direct activation of SAC_{NS} can be sufficient to trigger an AP in isolated cardiomyocytes at rest[10]. However, as cardiomyocyte membrane potential changes during the cardiac cycle, electrophysiological effects of acute mechanical stimulation depend on timing relative to the cardiac cycle (see also Chapter 14).

In this chapter we use the terms 'systole' and diastole' to distinguish key phases of the cardiac cycle. More specifically, and even though the terms were originally designated to describe mechanical behaviour, we follow the prevailing trend and use these terms to refer to the period of time during which ventricular cardiomyocytes are either at resting membrane potential (diastole) or inside the AP (systole).

Mechanical stimulation during diastole

If large enough to cause any change in potential at all, diastolic strain depolarizes the resting membrane of ventricular myocytes (Fig. 22.1). This has been demonstrated in isolated cells[11], tissue[12] and whole heart preparations[13].

In one of the classic MEC illustrations, Franz *et al.* showed in 1989 that transient increases in the volume of an intraventricular balloon cause diastolic depolarizations in isolated canine hearts[14]. The amplitude of these mechanically induced depolarizations correlates with the magnitude of volume changes applied. If sufficiently large, mechanically induced depolarizations can trigger premature ventricular contractions (PVC)[13] or short runs of VT[15]. This response has been attributed to SAC_{NS}, as their pharmacological block eliminates MEC responses in ventricular[16] and atrial[17] tissue (for more detail regarding acute stretch effects on atrial electrophysiology, see Chapter 23). Interestingly, the change in intraventricular volume required for arrhythmia induction is remarkably consistent between experiments in the same species, while the associated changes in intraventricular pressure show high variability. This suggests that myocardial strain (material deformation) may be a more important, though not exclusive, mediator of cardiac MEC responses compared to stress (force inside the material)[15].

Local ventricular mechanical stimulation, such as by fingertapping of the epicardium in open heart surgery or by external impacts to the precordium, can be used to pace the asystolic heart via diastolic depolarization-mediated MEC effects (see Chapter 50). As with changes in intraventricular volume, there is a threshold for

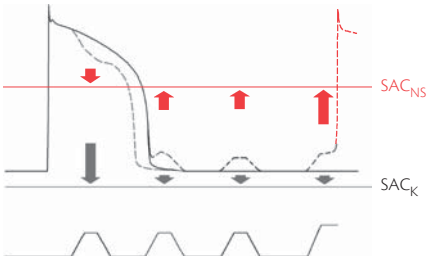

Fig. 22.1 Schematic representation of transient stretch effects on whole cell membrane potential and indication of contributions by cation non-selective and potassium-selective stretch-activated channels (SAC_{NS} and SAC_K, respectively). SAC_{NS} (red) have a reversal potential about half-way between action potential (AP) peak and resting potential (black curve). Depending on the timing of mechanical stimulation (bottom curve), their activation may shorten AP duration (grey dashed curve), cause behaviour reminiscent of early or delayed afterdepolarizations (EAD and DAD, respectively; black dashed curves) or – if strong enough – trigger a new AP (red dashed curve). The reversal potential of SAC_K (grey) is negative to the resting membrane potential. Their activation during *any* part of the cardiac cycle would tend to re- or hyperpolarize cardiac cells, in particular during the AP plateau when their electrotonic driving force is largest (compare lengths of arrows indicating SAC effects on membrane potential). [Reproduced, with permission, from Kohl P (2009) Cardiac stretch-activated channels and mechano-electric transduction. In: *Cardiac Electrophysiology: From Cell to Bedside* (eds D P Zipes, J Jalife). Saunders, Philadelphia, pp. 115–126.]

mechanical PVC induction, which has been established in healthy adult volunteers by defibrillation pioneer Paul Zoll as 0.04–1.50 J for precordial impacts[18]. For comparison, 0.1 J is equivalent to the impact energy of a 40 g glue stick dropped from a height of just under 30 cm (i.e. from your hand with the elbow resting on the table). This illustrates the exquisite mechano-sensitivity of the healthy, resting heart.

Mechanical stimulation during systole

The effects of systolic mechanical stimulation on cardiac electrophysiology are more varied (Fig. 22.1). During the AP plateau, activation of either SAC_{NS} or SAC_K will have a repolarizing effect on the cell. As a consequence, AP shortening has frequently been observed[19]. However, as the cell membrane repolarizes, it approaches, and eventually passes, the reversal potential of SAC_{NS}. This can give rise to prolongation of the AP[20], in particular at near-complete AP repolarization levels, and may find an expression in cross-over of the repolarization curve[21]. Furthermore, acute axial strain can cause early after-depolarization (EAD)-like events in isolated cardiomyocytes[22], which may underlie similar responses in multicellular experimental preparations[13,23]. Mechanically induced EAD-like depolarizations have also been reported in patients during balloon valvuloplasty, an intervention where the ventricular outflow tract is temporarily blocked, causing an increase in intraventricular pressure that can give rise to PVC[24].

Strain maintained beyond the end of the AP (and therefore acting somewhere at the cross-roads of electrical systole and diastole, according to the definition used in this chapter) can cause delayed after-depolarization (DAD)-like behaviour. This may also serve as a source of PVC induction which, in the presence of a suitably arrhythmogenic background (such as experimentally induced prolongation of the QT segment of the electrocardiogram, ECG), can contribute to the initiation of sustained arrhythmias (e.g. *torsades de pointes* in the anaesthetized dog)[25].

In addition to the variable effects of mechanical stimulation on the AP of individual cells, it must be noted that at the whole organ level 'electrical systole' is associated with significant spatial non-uniformity in membrane potential across the ventricular myocardium. This means that timing of a mechanical stimulus 'relative to the AP' will be different in different parts of the heart (Fig. 22.2). While the ventricular activation wave-front is steep and fast (leaving comparatively little room for regionally differing responses to mechanical stimulation; see narrow QRS complex of the ECG in Fig. 22.2), repolarization is a more graded process (broader and lower ECG T-wave). This gives rise to an additional temporal component at the organ level: a vulnerable window for mechanical induction of tachy-arrhythmias, which conceptually is very similar to the vulnerable window for electrical stimulation that was systematically established in the 1930s[26].

The vulnerable window for mechanical induction of ventricular fibrillation (VF) has been identified by Link *et al.* in an anaesthetized pig model of *Commotio cordis* to occur 15–30 ms before the peak of the ECG T-wave[27] (see Chapter 45). This behaviour can be linked to SAC_{NS} (Fig. 22.2). Their activation may give rise to DAD-like events (in cells that have regained excitability) or EAD-like behaviour (in cells that are repolarizing). If supra-threshold, these depolarizations can cause ectopic foci, potentially providing a trigger for arrhythmogenesis. SAC_{NS} activation in cells at more positive membrane potentials may affect the time-course of repolarization, increasing electrophysiological heterogeneity in affected areas of the myocardium, which could contribute to the formation of an arrhythmia-sustaining substrate for re-entry.

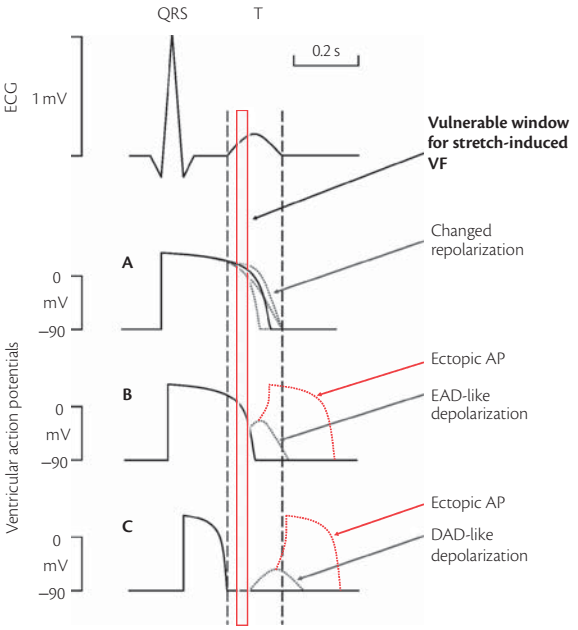

Fig. 22.2 Schematic representation of potentially arrhythmogenic SAC_{NS} effects during early repolarization (upstroke of the T-wave, see red box and electrocardiogram, ECG, at top). Regionally differing effects would be determined by locally differing stages of AP repolarization and include: **A** changes in AP duration such as shortening, prolongation or crossover of repolarization; **B** EAD-like behaviour; **C** DAD-like events. Both EAD- and DAD-like events may trigger ectopic excitation, while sub-threshold changes increase heterogeneity in the electrophysiological background behaviour, potentially contributing to arrhythmia sustenance. VF, ventricular fibrillation. [Reproduced, with permission, from Kohl P, Nesbitt AD, Cooper PJ, Lei M (2001) Sudden cardiac death by *Commotio cordis*: role of mechano-electric feedback. *Cardiovasc Res* **50**:280–289.]

Computational modelling has been helpful in assessing the quantitative *plausibility* of this concept. Using a two-dimensional (2D) model of ventricular tissue, Garny and Kohl[28] demonstrated that sustained re-entry is observed only if the mechanical stimulus (1) encounters excitable tissue (giving rise to an ectopic focus by cellular depolarization), (2) overlaps with the repolarization wave end (giving rise to an area of functional block by AP prolongation) and (3) extends into tissue with membrane potentials above the SAC_{NS} reversal potential (giving rise to an arrhythmia-sustaining substrate by regional AP shortening). In the model, this can occur during the second quarter of the T-wave (Fig. 22.3A). Impacts timed earlier or later in the cardiac cycle either are inefficient in triggering PVC or result in a single ectopic activation only, without sustained re-entry (Fig. 22.3B and C, respectively). While the situation will be more complex in a three-dimensional (3D) substrate such as the whole heart, similar results have been obtained using an anatomically detailed whole-ventricular model[29].

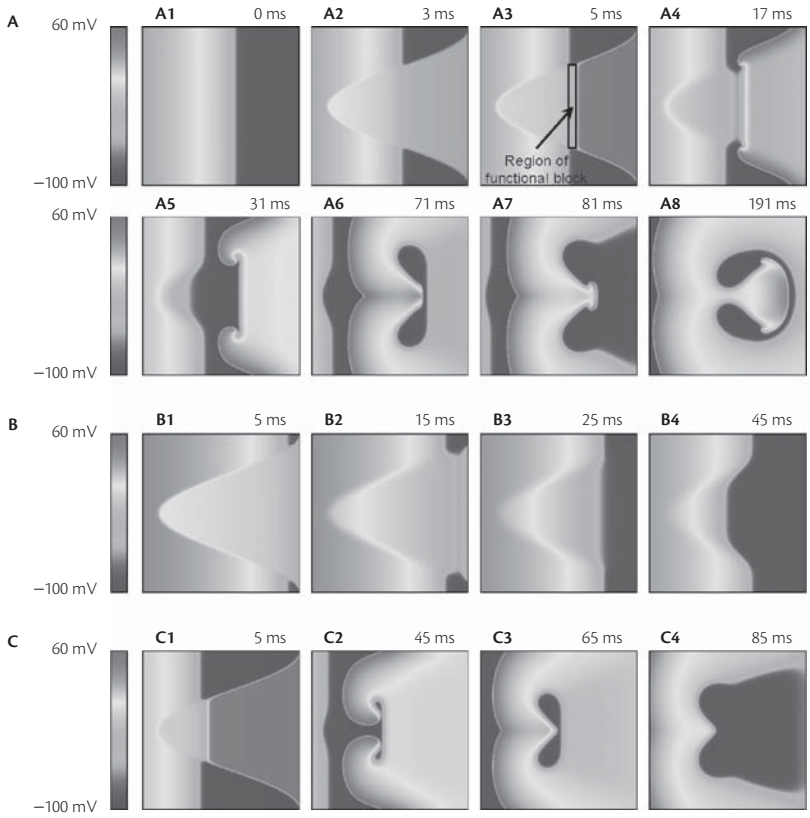

Fig. 22.3 Computer simulation of epicardial impact effects on ventricular electrophysiology. Impacts are simulated by 5 ms activation of SAC_{NS} in the area highlighted in A2 and applied at different stages of ventricular repolarization (i.e. during different times of the ECG T-wave). **A** Development of a mechanically induced sustained ventricular arrhythmia, following a simulated impact at 40% repolarization. Arrhythmia sustenance depends on supra-threshold mechanical stimulation that triggers an extra AP in tissue that has recovered from inactivation, and on overlap of the mechanically stimulated tissue region with the trailing wave of repolarization, where an area of functional block gives rise to wave-split. Arrhythmia sustenance is further favoured by partial repolarization of near-endocardial myocardium from AP plateau towards membrane potentials closer to the reversal potential of SAC_{NS}. **B** Lack of arrhythmogenic effect of impacts applied too early during repolarization (< 10% repolarization). **C** Single ectopic AP without subsequent re-entry, caused by later impacts (here at 60% repolarization). [Reproduced, with permission, from Garny A, Kohl P (2004) Mechanical induction of arrhythmias during ventricular repolarization: modeling cellular mechanisms and their interaction in two dimensions. *Ann N Y Acad Sci* **1015**:133–143.] (See color plate section.)

Even though the electrophysiological response to mechanical stimulation appears to be dominated, in healthy myocardium, by SAC_{NS} activation, there is experimental evidence in support of a contribution by certain SAC_K. In particular, a role for the mechano-sensitive[30,31] adenosine triphosphate-sensitive K^+ channel (K_{ATP}) has been demonstrated in the context of arrhythmias induced by precordial impact. Interestingly, mechanical and ischaemic activation of K_{ATP} channels has been reported to act co-operatively, helping to explain why some of the changes in electrocardiographic parameters after precordial impact (like ECG ST-segment elevation) mimic those commonly associated with myocardial ischaemia, even though there does not appear to be significant disturbance of coronary flow[27]. Equally, reduced K_{ATP} channel activation may be one of the mechanisms by which mechanical *prevention* of 'ischaemic bulging' can help to reduce extracellular potassium accumulation in the ischaemic myocardium (see Chapter 24). In whole animal studies of *Commotio cordis*, application of glibenclamide, a non-specific inhibitor of K_{ATP} channels, was found to significantly reduce VF induction, as well as ST segment elevation[32]. As impacts during the previously established vulnerable window still triggered PVC in the anaesthetized pig, the contribution of this particular SAC_K population is likely to support sustenance, rather than induction, of arrhythmias (it is also possible that their pharmacological block shifted the vulnerable window for VF induction).

Interestingly, application of streptomycin (an efficient blocker of SAC_{NS} in isolated cells) [33] had no effect on VF inducibility in the same model[34]. This raises the question as to what causes the impact-induced depolarization that underlies PVC, not only in diastole, but also during the T-wave (such as unmasked in the presence of glibenclamide). PVC arise in consequence of supra-threshold depolarization and may thus be caused either by mechanical activation of a

depolarizing SAC (such as SAC_{NS}) or by mechanical reduction of a hyperpolarizing SAC (such as SAC_K) in the presence of sufficient background depolarizing currents. Given that there is little evidence in support of the latter scenario, the question remains why streptomycin had no effect on mechanical VF induction *in vivo*. Potential explanations include contributions by a streptomycin-insensitive form of SAC_{NS}, or limited efficacy of streptomycin as an acute SAC blocker in the whole animal. The latter would seem plausible, based on the absence of acutely impeded mechano-reception in patients receiving the antibiotic (side effects on inner ear function, for example, are usually seen only after prolonged exposure to the antibiotic). Limited efficacy of streptomycin for acute SAC_{NS} block *in situ* has also been documented in previous experiments on sino-atrial node tissue, in which stretch responses were unaffected by high doses of the antibiotic, yet abolished by the peptide SAC_{NS} blocker *Grammostola spatulata* mechano-toxin 4 (GsTMx-4)[35]. Thus, further studies are required to elucidate the contribution of different SAC types to mechanical induction of ventricular tachy-arrhythmias.

Mechanically induced VF probability further depends on impact site, contact area, and projectile stiffness. Impacts in an area of close approximation between precordium and heart are more likely to initiate VF than others, smaller contact areas are more arrhythmogenic, and projectile stiffness is correlated with propensity to induce VF. All these observations highlight the importance of localized mechanical energy transfer, first noted in the 1930s by Schlomka, who reported that precordial impacts in larger animals held in supine position (where the heart is relieved of its intimate mechanical coupling to the chest wall) do not readily induce arrhythmias[36].

In addition to local effects, arrhythmogenic precordial impacts are also associated in whole animal studies with large, but brief, surges in intraventricular pressure. These could give rise to a mechanical stimulus that affects ventricular tissue in a more global manner. Indeed, studies by Link *et al.* demonstrate a Gaussian relationship between the amplitude of intraventricular pressure surges and VF probability, which was greatest at pressure levels between 250 and 450 mmHg, reaching 68% at ~ 350 mmHg[37]. An interesting aspect of these data is that amplitude and *duration* of pressure surges are likely to be correlated; whether there is an independent contribution of the duration of intraventricular pressure changes remains to be investigated. Equally, the individual importance of global vs regional mechanical effects on cardiac electrical activity deserves more detailed consideration.

Effects of acute mechanical stimulation on heart rhythm: spatial aspects

General considerations

Increases in intraventricular volume or pressure, whether induced by intrinsic mechanisms that affect pre- or afterload or by causes extrinsic to the cardiovascular system such as intraventricular balloon inflation, can give rise to global strain of the ventricular tissue. However, myocardial compliance varies throughout the ventricles, due to the anisotropy of structural, active contractile, and passive viscoelastic properties. Therefore, 'globally uniform' mechanical stimulation can result in 'regionally heterogeneous' MEC effects. At the same time, more localized interventions such as precordial impact are associated with an increase in ventricular pressure, which may induce more globally acting responses. Thus, in many settings, global and regional MEC effects will coincide, making identification of their individual contributions to arrhythmogenesis difficult.

Global mechanical stimulation

Some of the earliest *ex situ* whole heart investigations into the effects of mechanical stimulation on electrical behaviour used intraventricular balloons to apply global ventricular volume loads[14]. More recently, intraventricular balloons have been used in Langendorff-perfused hearts to simulate the pressure surges seen in whole animal models of *Commotio cordis*. Bode *et al.* found that large changes in intraventricular volume can induce VF in isolated rabbit hearts, in a magnitude- and (ECG) timing-dependent manner[38]. Pressure pulses between 209 and 289 mmHg were capable of inducing VF in 11% of cases where the stimulus was applied within a vulnerable window that was phenomenologically similar to that described for precordial impact[37].

The biophysical characteristics of pressure surges during precordial impact (ultra-fast pressure transients that occur in the absence of causal intraventricular volume alterations, with optimal VF induction at a peak-rate of ventricular pressure change, dP/dt_{max}, of 50 mmHg × ms^{-1})[37] are not easily reproduced by volume-pulsing of isolated hearts. Conceptually, the former may be regarded as an intervention where local stress (or strain) causes a global change in mechanics (pressure surge), while the latter is based on a global intervention (more slowly occurring volume pulse) which is translated into regionally heterogeneous stress-strain patterns. During volume loading, heterogeneity of myocardial structure and viscoelasticity will result in regional variation of tissue strain, giving rise to spatio-temporal dissociation between the globally uniform stimulus and its regional representation.

The response of cardiac muscle to ultra-fast pressure surges (few milliseconds duration) in the absence of volume loading may be even more complex, as such short-lived pressure surges may be too brief to cause effective tissue strain (buffered by myocardial viscosities). This may create peak stress levels that cause local tissue damage, even at pressure levels that would be tolerated in steady-state conditions, and should be assessed in future research.

The importance of regionally heterogeneous effects of global stimulation *in vivo* is supported by the observation that diastolic increases in intraventricular volume yield non-uniform depolarization, with the origin of ectopic AP induction most often in the postero-lateral region of the left ventricle, typically a region of high compliance[13]. More recently, Seo *et al.* have shown that stretch, applied across a flap of right ventricular tissue, gives rise to focal excitation at the point of the largest differences in strain, resulting in sustained tachy-arrhythmias[39]. Thus, regional heterogeneity of globally uniform mechanical stimulation appears to be a key contributor to arrhythmogenesis. In fact, in the computational model by Garny and Kohl[28], simultaneous activation of SAC_{NS} in the entire tissue block does not result in re-entry. If it captures all tissue that has regained excitability, a single ectopic beat, forming a planar wave, is caused (data not shown). So, in the absence of heterogeneity beyond the already pre-existing repolarization-related regional differences, mechanical stimulation is much less arrhythmogenic compared to scenarios where either the mechanical stimulus or its effects at the tissue level differ across the heart.

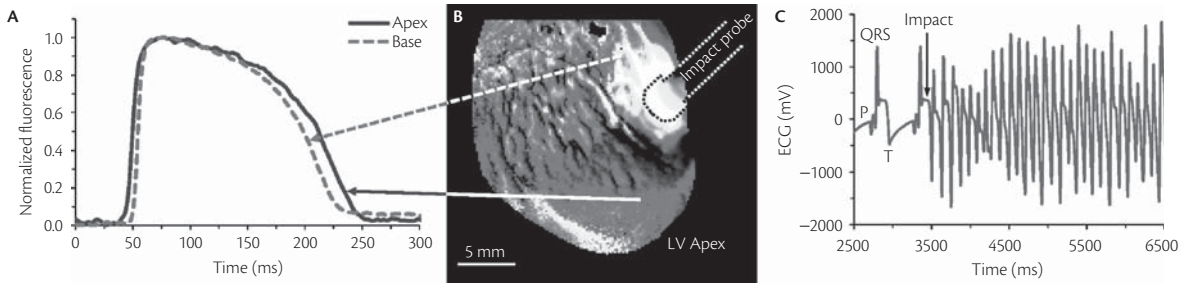

Fig. 22.4 Focal activation and ventricular fibrillation (VF) induced by local non-traumatic impacts in Langendorff-perfused rabbit hearts. **A** Spatial AP differences, visualized by epicardial optical voltage mapping, illustrate apico-basal activation delay during normal sinus rhythm and progression of the repolarization wave in the opposite direction. **B** Diastolic impact using a precision-controlled probe at energy levels < 1 mJ cause focal activation, followed by ectopic excitation of the ventricles. **C** Impact during the early T-wave causes focal excitation, followed by VF. This behaviour occurs when there is spatio-temporal overlap of the repolarization wave and mechanically stimulated tissue. [Reproduced, with permission, from Quinn TA, Lee P, Bub G, Epstein A, Kohl P (2010) Regional impact-induced arrhythmia in isolated rabbit heart visualised by optical mapping. *Heart Rhythm* **7**:S353.] (See color plate section.)

Regional mechanical stimulation

Regional mechanical stimulation may play an important role for arrhythmogenesis in diseases that involve heterogeneous changes in ventricular compliance, such as regional ischaemia[40] and infarction[41]. In both settings there is an increase in the probability of excitation in areas of particularly high strain gradients, such as via paradoxical segment lengthening of ischaemic tissue or at the scar–myocardial tissue interface of infarcts. In fact, the degree of dilation of an ischaemic region is a strong predictor of arrhythmia probability, including VF[42]. 3D computational modelling suggests that premature ventricular excitation originates, in this setting, from the ischaemic border zone, where mechanically induced depolarizations may contribute to the formation of ectopic foci (if supra-threshold) or to the slowing and block of conduction (if sub-threshold)[43]. Similarly, in VF, localized strain increases the complexity of activation maps in the affected region, with more areas of conduction block and transmural excitation breakthrough sites[44]. These results support the hypothesis that local strain gradients, whether applied regionally or resulting from heterogeneous translation of global mechanical perturbations, play important roles in the initiation and sustenance of re-entrant arrhythmias.

Still, quantitative discrimination between MEC effects of mechanical stimulation with primarily global or primarily local character remains a challenging task for further research. One published endocardial activation sequence, recorded in a single pig experiment during precordial impact-induced VF, shows focal excitation of the ventricle directly underneath the site of impact[45] (see Fig. 46.3). This might suggest that local effects are relevant even in the setting of *Commotio cordis*. Our own preliminary optical mapping studies demonstrate focal activation during non-traumatic epicardial impacts[46], applied to Langendorff-perfused rabbit hearts using a local impactor[47] (Fig. 22.4). In this setting, ectopic ventricular excitation can induce VF when there is spatio-temporal overlap of the mechanically stimulated tissue with the receding wave of previous excitation[46], confirming experimentally prior modelling-based predictions.

Conclusions and outlook

Acute mechanical stimulation can cause ventricular tachy-arrhythmias, by providing a trigger (ectopic excitation) and by creating or enhancing arrhythmia-sustaining mechanisms. The molecular substrates of this behaviour are believed to include SAC, and SAC_{NS} in particular are contenders for the mechanism underlying mechanical AP induction. Additional activation of SAC_K is likely to form one of the mechanisms that help to sustain tachy-arrhythmic responses. Further examination of the precise contributions of different SAC populations call for studies in which global *versus* regional ventricular strain effects can be controlled, or at least monitored, and where the activity of SAC_{NS} and SAC_K can be pharmacologically manipulated with confirmed efficacy and specificity in native tissue. Novel non-invasive imaging approaches, combined with individualized quantitative computational modelling, will increasingly allow one to link the characterization of 'global' descriptors of cardiac mechano-electric activity (e.g. intra-ventricular volume or pressure changes or ECG) to 'regional' behaviour (e.g. transmural stress-strain distributions or high-resolution endo- or epicardial electrical activation and repolarization maps)[48]. This will be an important step towards linking cellular and sub-cellular MEC responses to spatio-temporal variations in ventricular stress-strain patterns, identifying molecular mechanisms that underlie ventricular function in three-dimensions and time.

References

1. Kohl P, Hunter P, Noble D. Stretch-induced changes in heart rate and rhythm: clinical observations, experiments and mathematical models. *Prog Biophys Mol Biol* 1999;**71**:91–138.
2. Lab MJ. Contraction–excitation feedback in myocardium. Physiological basis and clinical relevance. *Circ Res* 1982;**50**:757–766.
3. Waxman MB, Wald RW, Finley JP, Bonet JF, Downar E, Sharma AD. Valsalva termination of ventricular tachycardia. *Circulation* 1980;**62**:843–851.
4. Ambrosi P, Habib G, Kreitmann B, Faugere G, Metras D. Valsalva manoeuvre for supraventricular tachycardia in transplanted heart recipient. *Lancet* 1995;**346**:713.

5. Craelius W, Chen V, el-Sherif N. Stretch activated ion channels in ventricular myocytes. *Biosci Rep* 1988;**8**:407–414.
6. Sigurdson WJ, Morris CE, Brezden BL, Gardner DR. Stretch activation of a potassium channel in molluscan heart cells. *J Exp Biol* 1987;**127**:191–210.
7. Sachs F. Mechanical transduction by membrane ion channels: a mini review. *Mol Cell Biochem* 1991;**104**:57–60.
8. Sackin H. Stretch-activated ion channels. *Kidney Int* 1995;**48**: 1134–1147.
9. Morris CE. Mechanosensitive ion channels. *J Membr Biol* 1990;**113**: 93–107.
10. Craelius W. Stretch-activation of rat cardiac myocytes. *Exp Physiol* 1993;**78**:411–423.
11. White E, Boyett MR, Orchard CH. The effects of mechanical loading and changes of length on single guinea-pig ventricular myocytes. *J Physiol* 1995;**482**:93–107.
12. Lab MJ. Depolarization produced by mechanical changes in normal and abnormal myocardium [proceedings]. *J Physiol* 1978;**284**(Suppl):143P–144P.
13. Franz MR, Cima R, Wang D, Profitt D, Kurz R. Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. *Circulation* 1992;**86**:968–978.
14. Franz MR, Burkhoff D, Yue DT, Sagawa K. Mechanically induced action potential changes and arrhythmia in isolated and in situ canine hearts. *Cardiovasc Res* 1989;**23**:213–223.
15. Hansen DE, Craig CS, Hondeghem LM. Stretch-induced arrhythmias in the isolated canine ventricle. Evidence for the importance of mechanoelectrical feedback. *Circulation* 1990;**81**:1094–1105.
16. Hansen DE, Borganelli M, Stacy GP, Taylor LK. Dose-dependent inhibition of stretch-induced arrhythmias by gadolinium in isolated canine ventricles. Evidence for a unique mode of antiarrhythmic action. *Circ Res* 1991;**69**:820–831.
17. Bode F, Sachs F, Franz MR. Tarantula peptide inhibits atrial fibrillation. *Nature* 2001;**409**:35–36.
18. Zoll PM, Belgard AH, Weintraub MJ, Frank HA. External mechanical cardiac stimulation. *N Engl J Med* 1976;**294**:1274–1275.
19. White E, Le Guennec JY, Nigretto JM, Gannier F, Argibay JA, Garnier D. The effects of increasing cell length on auxotonic contractions; membrane potential and intracellular calcium transients in single guinea-pig ventricular myocytes. *Exp Physiol* 1993;**78**: 65–78.
20. Zeng T, Bett GC, Sachs F. Stretch-activated whole cell currents in adult rat cardiac myocytes. *Am J Physiol* 2000;**278**:H548–H557.
21. Zabel M, Koller BS, Franz MR. Amplitude and polarity of stretch-induced systolic and diastolic voltage changes depend on the timing of stretch: a means to characterize stretch-activated channels in the intact heart. *Pacing Clin Electrophysiol* 1993;**16**:886.
22. Kohl P (2009). Cardiac stretch-activated channels and mechano-electric transduction. In: *Cardiac Electrophysiology: From Cell to Bedside* (eds D.P. Zipes, J. Jalife). Saunders, Philadelphia, pp. 115–126.
23. Nazir SA, Lab MJ. Mechanoelectric feedback in the atrium of the isolated guinea-pig heart. *Cardiovasc Res* 1996;**32**:112–119.
24. Levine JH, Guarnieri T, Kadish AH, White RI, Calkins H, Kan JS. Changes in myocardial repolarization in patients undergoing balloon valvuloplasty for congenital pulmonary stenosis: evidence for contraction–excitation feedback in humans. *Circulation* 1988;**77**: 70–77.
25. Gallacher DJ, Van de Water A, van der Linde H, *et al.* In vivo mechanisms precipitating torsades de pointes in a canine model of drug-induced long-QT1 syndrome. *Cardiovasc Res* 2007;**76**: 247–256.
26. Wiggers CJ, Wégria R. Ventricular fibrillation due to single, localized induction and condenser shocks applied during the vulnerable phase of ventricular systole. *Am J Physiol* 1940;**128**:500–505.
27. Link MS, Wang PJ, Pandian NG, *et al.* An experimental model of sudden death due to low-energy chest-wall impact (*Commotio cordis*). *N Engl J Med* 1998;**338**:1805–1811.
28. Garny A, Kohl P. Mechanical induction of arrhythmias during ventricular repolarization: modeling cellular mechanisms and their interaction in two dimensions. *Ann N Y Acad Sci* 2004;**1015**: 133–143.
29. Li W, Kohl P, Trayanova N. Induction of ventricular arrhythmias following mechanical impact: a simulation study in 3D. *J Mol Histol* 2004;**35**:679–686.
30. Van Wagoner DR. Mechanosensitive gating of atrial ATP-sensitive potassium channels. *Circ Res* 1993;**72**:973–983.
31. Van Wagoner DR, Lamorgese M. Ischemia potentiates the mechanosensitive modulation of atrial ATP-sensitive potassium channels. *Ann N Y Acad Sci* 1994;**723**:392–395.
32. Link MS, Wang PJ, VanderBrink BA, *et al.* Selective activation of the K_{ATP} channel is a mechanism by which sudden death is produced by low-energy chest-wall impact (*Commotio cordis*). *Circulation* 1999;**100**:413–418.
33. Belus A, White E. Streptomycin and intracellular calcium modulate the response of single guinea-pig ventricular myocytes to axial stretch. *J Physiol* 2003;**546**:501–509.
34. Garan AR, Maron BJ, Wang PJ, Estes NA, 3rd, Link MS. Role of streptomycin-sensitive stretch-activated channel in chest wall impact induced sudden death (*Commotio cordis*). *J Cardiovasc Electrophysiol* 2005;**16**:433–438.
35. Cooper PJ, Kohl P. Species- and preparation-dependence of stretch effects on sino-atrial node pacemaking. *Ann N Y Acad Sci* 2005;**1047**:324–335.
36. Schlomka G. *Commotio cordis* und ihre Folgen. Die Einwirkung stumpfer Brustwandtraumen auf das Herz. *Ergebn Inn Med Kinderheilkd* 1934;**47**:1–91.
37. Link MS, Maron BJ, Wang PJ, VanderBrink BA, Zhu W, Estes NA, 3rd. Upper and lower limits of vulnerability to sudden arrhythmic death with chest-wall impact (*Commotio cordis*). *J Am Coll Cardiol* 2003;**41**:99–104.
38. Bode F, Franz M, Wilke I, Bonnemeier H, Schunkert H, Wiegand U. Ventricular fibrillation induced by stretch pulse: implications for sudden death due to *Commotio cordis. J Cardiovasc Electrophysiol* 2006;**17**:1011–1017.
39. Seo K, Inagaki M, Nishimura S, *et al.* Structural heterogeneity in the ventricular wall plays a significant role in the initiation of stretch-induced arrhythmias in perfused rabbit right ventricular tissues and whole heart preparations. *Circ Res* 2010;**106**:176–184.
40. Parker KK, Lavelle JA, Taylor LK, Wang Z, Hansen DE. Stretch-induced ventricular arrhythmias during acute ischemia and reperfusion. *J Appl Physiol* 2004;**97**:377–383.
41. Fu L, Cao JX, Xie RS, *et al.* The effect of streptomycin on stretch-induced electrophysiological changes of isolated acute myocardial infarcted hearts in rats. *Europace* 2007;**9**:578–584.
42. Barrabes JA, Garcia-Dorado D, Padilla F, *et al.* Ventricular fibrillation during acute coronary occlusion is related to the dilation of the ischemic region. *Basic Res Cardiol* 2002;**97**: 445–451.
43. Jie X, Gurev V, Trayanova N. Mechanisms of mechanically induced spontaneous arrhythmias in acute regional ischemia. *Circ Res* 2010;**106**:185–192.
44. Chorro FJ, Trapero I, Guerrero J, *et al.* Modification of ventricular fibrillation activation patterns induced by local stretching. *J Cardiovasc Electrophysiol* 2005;**16**:1087–1096.
45. Alsheikh-Ali AA, Akelman C, Madias C, Link MS. Endocardial mapping of ventricular fibrillation in *Commotio cordis. Heart Rhythm* 2008;**5**:1355–1356.

46. Quinn TA, Lee P, Bub G, Epstein A, Kohl P. Regional impact-induced arrhythmia in isolated rabbit heart visualised by optical mapping. *Heart Rhythm* 2010;**7**(5S):S353.
47. Cooper PJ, Epstein A, Macleod IA, *et al.* Soft tissue impact characterisation kit (STICK) for ex situ investigation of heart rhythm responses to acute mechanical stimulation. *Prog Biophys Mol Biol* 2006;**90**:444–468.
48. Plank G, Burton RA, Hales P, *et al.* Generation of histo-anatomically representative models of the individual heart: tools and application. *Phil Trans R Soc (Lond.) A* 2009;**367**:2257–2292.