Original Article

Mechanically Induced Ectopy via Stretch-Activated Cation-Nonselective Channels Is Caused by Local Tissue Deformation and Results in Ventricular Fibrillation if Triggered on the Repolarization Wave Edge (Commotio Cordis)

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Background—External chest impacts (commotio cordis) can cause mechanically induced premature ventricular excitation (PVE_M) and, rarely, ventricular fibrillation (VF). Because block of stretch-sensitive ATP-inactivated potassium channels curtailed VF occurrence in a porcine model of commotio cordis, VF has been suggested to arise from abnormal repolarization caused by stretch activation of potassium channels. Alternatively, VF could result from abnormal excitation by PVE_M, overlapping with normal repolarization-related electric heterogeneity. Here, we investigate mechanisms and determinants of PVE_M induction and its potential role in commotio cordis–induced VF.

Methods and Results—Subcontusional mechanical stimuli were applied to isolated rabbit hearts during optical voltage mapping, combined with pharmacological block of ATP-inactivated potassium or stretch-activated cation-nonselective channels. We demonstrate that local mechanical stimulation reliably triggers PVE_M at the contact site, with inducibility predicted by local tissue indentation. PVE_M induction is diminished by pharmacological block of stretch-activated cation-nonselective channels. In hearts where electrocardiogram T waves involve a well-defined repolarization edge traversing the epicardium, PVE_M can reliably provoke VF if, and only if, the mechanical stimulation site overlaps the repolarization wave edge. In contrast, application of short-lived intraventricular pressure surges neither triggers PVE_M nor changes repolarization. ATP-inactivated potassium channel block has no effect on PVE_M inducibility per se, but shifts it to later time points by delaying repolarization and prolonging refractoriness.

Conclusions—Local mechanical tissue deformation determines PVE_M induction via stretch-activation of cation-nonselective channels, with VF induction requiring PVE_M overlap with the trailing edge of a normal repolarization wave. This defines a narrow, subject-specific vulnerable window for commotio cordis–induced VF that exists both in time and in space. (*Circ Arrhythm Electrophysiol*. 2017;10:e004777. DOI: 10.1161/CIRCEP.116.004777.)

Key Words: arrhythmia ■ blebbistatin ■ electrophysiology ■ heart ■ mechanoreceptors

For over a century, it has been known that the heart is an exquisitely mechanosensitive organ.[1] Subcontusional mechanical stimulation of the heart (commotio cordis [CC]), whether by intracardiac device/tissue interactions or by chest impacts, can result in a variety of heart rhythm changes, including ectopy (eg, mechanically induced premature ventricular excitation [PVE_M]) and sustained rhythm disturbances (eg, ventricular fibrillation [VF]).[2]

PVE_M is common in patients with central monitoring catheters[3,4] or intracardiac pacing wires.[5–7] It is also presumed to be common in CC-prone sports, such as baseball or ice hockey, and CC-induced VF is one of the most common causes of

death in youth athletes in the United States.[8] However, mechanisms of PVE_M genesis and determinants for VF induction are ill-understood.

What is known is that stretch can trigger PVE_M in myocardial cells,[9] tissue,[10] and whole heart.[11] This mechano-electric feedback[12–14] can be explained by stretch-activated cation-nonselective channels (SAC_{NS}),[15] which depolarize diastolic transmembrane potential (V_m) in cardiomyocytes[16] and whole hearts.[17] During the action potential (AP) plateau, stretch accelerates V_m repolarization by activating SAC_{NS}[17,18] (their reversal potential is approximately half-way between peak and resting V_m levels[19]) or by opening stretch-sensitive

potassium-selective currents,[20] causing early AP shortening. In CC, the mechanosensitive ATP-inactivated potassium (K_{ATP}) current[21] has been implicated in VF induction, as administration of glibenclamide (a nonspecific K_{ATP} blocker) reduced mechanical VF induction in a porcine model of CC.[22]

Electrophysiological outcomes of CC are modulated by mechanical stimulus characteristics, such as location, area, and duration.[23] Studies in the porcine model have characterized mechanical inducibility of VF as inversely related to impact area and duration, rising with projectile stiffness and, most strikingly, occurring only during a narrow vulnerable period: 15 to 30 ms before the ECG T-wave peak.[8,24,25]

Generally, VF vulnerability during the T wave is related to repolarization dynamics. In the case of locally acting mechanical stimuli, as ventricular repolarization is spatially nonuniform, timing relative to the ECG will not translate into a similarly defined timing relative to the V_m of affected cardiomyocytes.[26] Computational simulations have suggested that mechanically induced VF can occur only when a suprathreshold mechanical stimulus occurs at the trailing edge of the preceding normal repolarization wave.[27,28] In this situation, PVE_M in excitable tissue arises directly adjacent to refractory tissue, resulting in a region of functional conduction block around which reentry can ensue. As a wave of repolarization travels across the ventricles, the condition for such overlap will be met in different locations at different times, and for very brief periods only. From this site dependence of critical mechanical

stimulation timing follows the hypothesis that the vulnerable window for CC-induced VF exists both in time and in space. Experimental assessment of this computationally predicted mechanism is still outstanding.

An interesting additional question concerns the role of the large, but short-lived, intraventricular pressure surge that accompanies precordial impacts. In a porcine CC model, VF-inducing impacts cause pressure surges whose amplitude correlates with both impact severity and probability of VF induction.[29] Yet similarly pronounced intraventricular pressure surges are seen with coughing,[30] where they are not normally associated with induction of sustained arrhythmias. Therefore, the question as to whether the intraventricular pressure surge is causal for CC-induced VF, or is a covariate of those impact properties that determine arrhythmogenicity, requires experimental verification.

Thus, the goals of our study were to assess, in the Langendorff-perfused rabbit heart (in which mechanoelectric feedback responses are well preserved[31]), mechanisms of PVE_M induction, and their potential role in triggering VF. Our specific aims were to determine whether (1) PVE_M induction depends on the degree of local tissue deformation, deformation rate, applied force, stress, or intraventricular pressure surges; (2) CC effects on cardiac electrophysiology are caused by SAC_{NS} or mechanosensitive K_{ATP}; and (3) spatiotemporal overlap of mechanical stimulation with the trailing edge of the repolarization wave is critical for VF induction. These aims were addressed by controlled application of subcontusional local epicardial mechanical stimuli, or intraventricular volume bursts, during optical V_m mapping in the absence or presence of suitable pharmacological blockers of SAC_{NS} or K_{ATP}.

Methods

Ethical Approval

This study was performed, under local ethical approval, in strict accordance with the UK Home Office Animals (Scientific Procedures) Act of 1986. Details of experimental protocols have been reported following the Minimum Information About a Cardiac Electrophysiology Experiment reporting standard,[32] repository (https://www.micee.org/?q=node/00001374). Detailed methods are given in the Data Supplement.

Heart Preparation

Langendorff-perfused hearts from female New Zealand White rabbits were instrumented with custom-made polyethylene balloons in the left ventricle (LV) connected to a transducer for the measurement of intraventricular pressure and a servomotor-controlled syringe for rapid bidirectional volume alteration. Surface ECG was recorded using 2 spring-loaded monopolar Ag/AgCl pellet electrodes. The experimental setup can be seen in Figure I in the Data Supplement.

Voltage Optical Mapping

Hearts were loaded with a voltage-sensitive dye (di-4-ANBDQPQ) and an electromechanical uncoupler (blebbistatin). Optical mapping was performed with a previously described system using light-emitting diodes for illumination and a 511 frames/s camera for observation.[33]

Mechanical Stimulation

Local mechanical stimuli were applied to the ventricular epicardium using the Soft Tissue Impact Characterisation Kit,[34] with the area of

indentation determined by impact probe surface and the magnitude of indentation monitored at ≈35 μm resolution using an optical grating. Images and characteristics of a typical stimulation are shown in Figure 1 and Movie I in the Data Supplement. For all stimuli, local excitation was assessed by optical V_m mapping. Intraventricular pressure surges were applied by brief bursts in intraventricular balloon volume (active inflation and deflation). Local mechanical stimulation and pressure surge timing relative to the ECG were controlled. Tissue integrity was assessed by analysis of creatine kinase activity in coronary effluent.[34]

Experimental Protocols

Four experimental series were performed.

Series 1 tested inducibility of PVE_M and VF by local mechanical stimulation (n=32; n=number of heart preparations). Subcontusional mechanical stimuli of ≈0.5 mJ were applied to 3.1 mm² contact areas across the LV freewall, and additional locations in some of these hearts: LV apex (n=4); LV base (n=4); LV/right ventricular (RV) border (n=4); and RV freewall (with an RV intraventricular balloon, n=11). Coupling interval to the preceding sinus beat was shortened (5 ms steps) from late diastole until either VF was induced or PVE_M ceased to be elicited (entering the electric refractory period).

Series 2 investigated determinants of PVE_M threshold and compared properties of mechanically and electrically induced ventricular excitation (n=7). In all hearts, local mechanical stimuli were applied to various locations of the LV and RV freewall using 3.1 or 28.3 mm² probes in randomized order during late diastole (at ≈75% of the cycle length). Stimulation energy was reduced from ≈0.5 mJ until PVE_M ceased to occur (ie, when below threshold). At each of the mechanically targeted LV locations, hearts were stimulated electrically, using a concentric bipolar stimulation electrode.

Series 3 assessed the roles of SAC_{NS} and K_{ATP} channels in mechanically induced responses using pharmacological blockers of SAC_{NS} (50, 250, and 500 μmol/L streptomycin, n=6; 500 nmol/L *Grammostola spatulata* MechanoToxin-4, n=5) and K_{ATP} channels (5 and 10 μmol/L glibenclamide, n=6).

Series 4 examined electrophysiological effects of intraventricular pressure surges (n=6). A rapid change in LV balloon volume (20 μL), producing pressure amplitudes that mimicked those seen during ≈0.5 mJ epicardial mechanical stimulation, was applied by active balloon inflation and deflation during diastole. This was repeated with volumes raised by 22 μL increments, normally up to a maximum of 130 μL.

Statistics

Data analysis was performed using custom programs in Matlab. Values are presented as mean±SD. For statistical tests, $P<0.05$ was taken to signify statistically significant differences between means. Comparison of local mechanically and electrically induced excitation and the effects of glibenclamide application were assessed by Wilcoxon signed-rank test (as distribution normality cannot be assumed). Mechanical stimulation characteristics at PVE_M threshold were compared by 1-way ANOVA with Tukey–Kramer post hoc test. Linear correlation between the change in intraventricular balloon volume and pressure surge amplitude, rise time, or fall time was assessed by Pearson correlation.

Results

PVE_M and VF Induction

All local mechanical stimuli applied to the ventricular epicardium with an amplitude of ≈0.5 mJ and a coupling interval
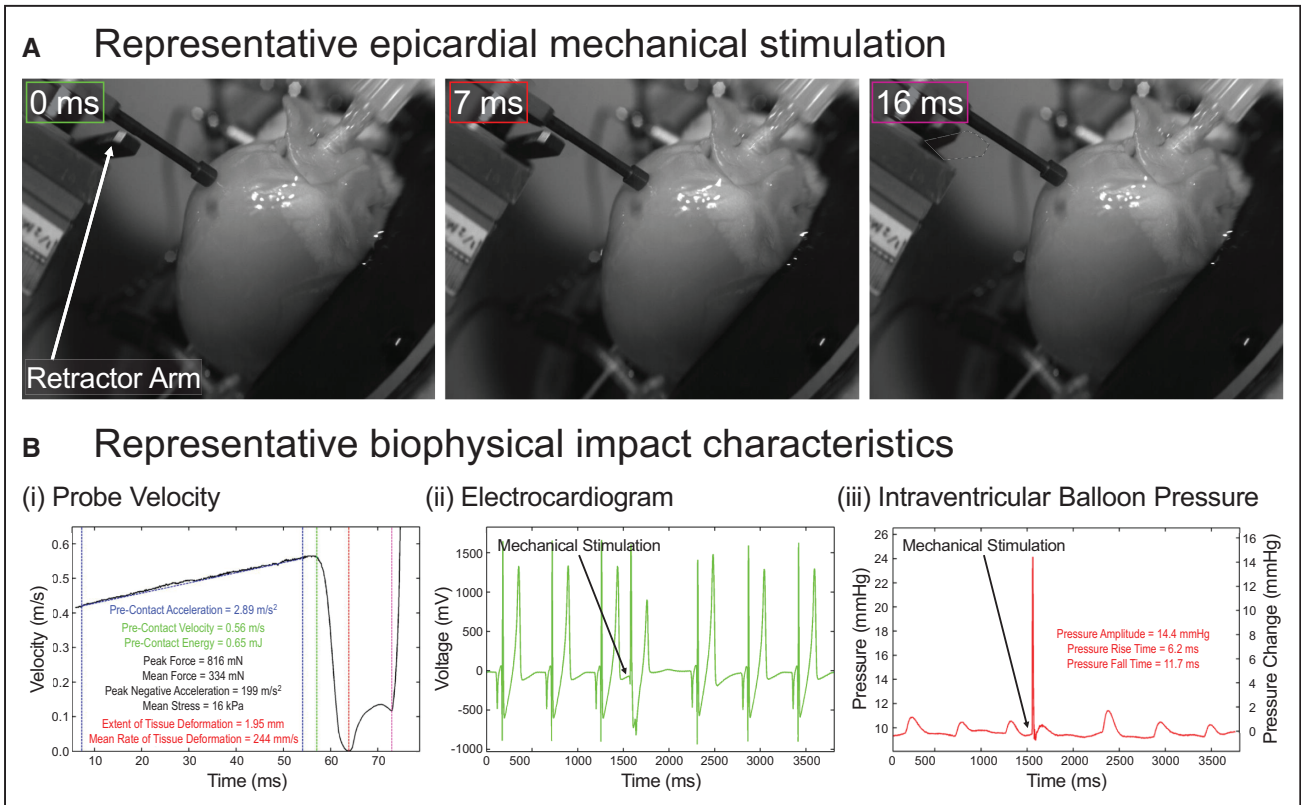
Figure 1. Subcontusional local epicardial mechanical stimulation. **A**, Images of a typical epicardial mechanical stimulus (from Movie I in the Data Supplement). **B**, Mechanical stimulation characteristics, showing: (i) probe velocity (blue lines indicate period of probe acceleration; green, red, and purple lines show time of initial tissue contact [0 ms in **A**], full probe deceleration [7 ms in **A**] followed by reversal of probe direction initially by tissue recoil, and subsequently by retractor arm activation [16 ms in **A**, dashed outline showing resting arm position]), along with calculated precontact probe acceleration, velocity, and kinetic energy; peak and mean force; peak negative acceleration; mean stress; and extent and mean rate of tissue deformation (Methods in the Data Supplement for calculations); (ii) surface ECG showing mechanically induced premature ventricular excitation; and (iii) intraventricular balloon pressure, along with impact-induced pressure surge amplitude and rise/fall times.

outside the refractory period (n=32 hearts; m=409 stimuli analyzed, all with confirmed lack of elevated creatine kinase activity), irrespective of stimulation location, resulted in PVE_M. This was associated with a change in activation pattern compared with sinus rhythm (compare Figure 2A and 2B) which, in terms of epicardially mapped V_m dynamics, generally propagated in an apicobasal direction, frequently involving multiple sites of epicardial breakthrough (Figure 2A; Movie II in the Data Supplement). In 6 of these hearts, the inducibility of PVE_M was also tested before the application of blebbistatin (ie, while still beating), which similarly showed 100% incidence (m=60), demonstrating that PVE_M induction is not conditional on electromechanical uncoupling.

All PVE_M, including those in the absence of an electromechanical uncoupler, originated focally from the stimulation site, confirmed by optical mapping (Figure 2B; Movie III in the Data Supplement). Mechanically and electrically induced ventricular excitation, triggered at the same location, resulted in downstream patterns of electric activation (compare Figure 2B and 2C; Movies III and IV in the Data Supplement) more similar to one another than to sinus activation (dV_m/dt_{max}, AP duration, and conduction velocity are given in the Table; n=6, m=18).

Most PVE_M-inducing stimuli resulted in a single ventricular activation. In 3 of 32 hearts, local mechanical stimulation

during the T wave gave rise to instantaneous induction of VF (Figure 3A; Movie V in the Data Supplement). VF episodes lasted 30 to 60 s before spontaneously converting to sinus rhythm. Where observed, mechanically induced VF was repeatable (m=13), when stimulation site and coupling interval were kept constant (including attempts with reduced mechanical stimulation energy, as long as suprathreshold for PVE_M, m=5).

In all cases of VF induction, optical mapping showed a well-defined trailing edge of the preceding depolarization wave, traversing the epicardial surface at the time of mechanical stimulation (Movie V in the Data Supplement). VF-inducing PVE_M induction sites corresponded to the 50% repolarization isochrone (Figure 3B), supporting previous 2-dimensional (Figure 3C)[27] and 3-dimensional[28] computational model predictions. A different repolarization pattern, near-uniform repolarization of the epicardial surface (Movie II in the Data Supplement), was seen in the other ≈90% of hearts. In these preparations, PVE_M did not cause VF at any coupling interval or impact location.

Determinants of PVE_M Threshold
For mechanical stimuli, applied during late diastole to either the LV or RV freewall using different probe contact areas, PVE_M threshold corresponded to significantly different values
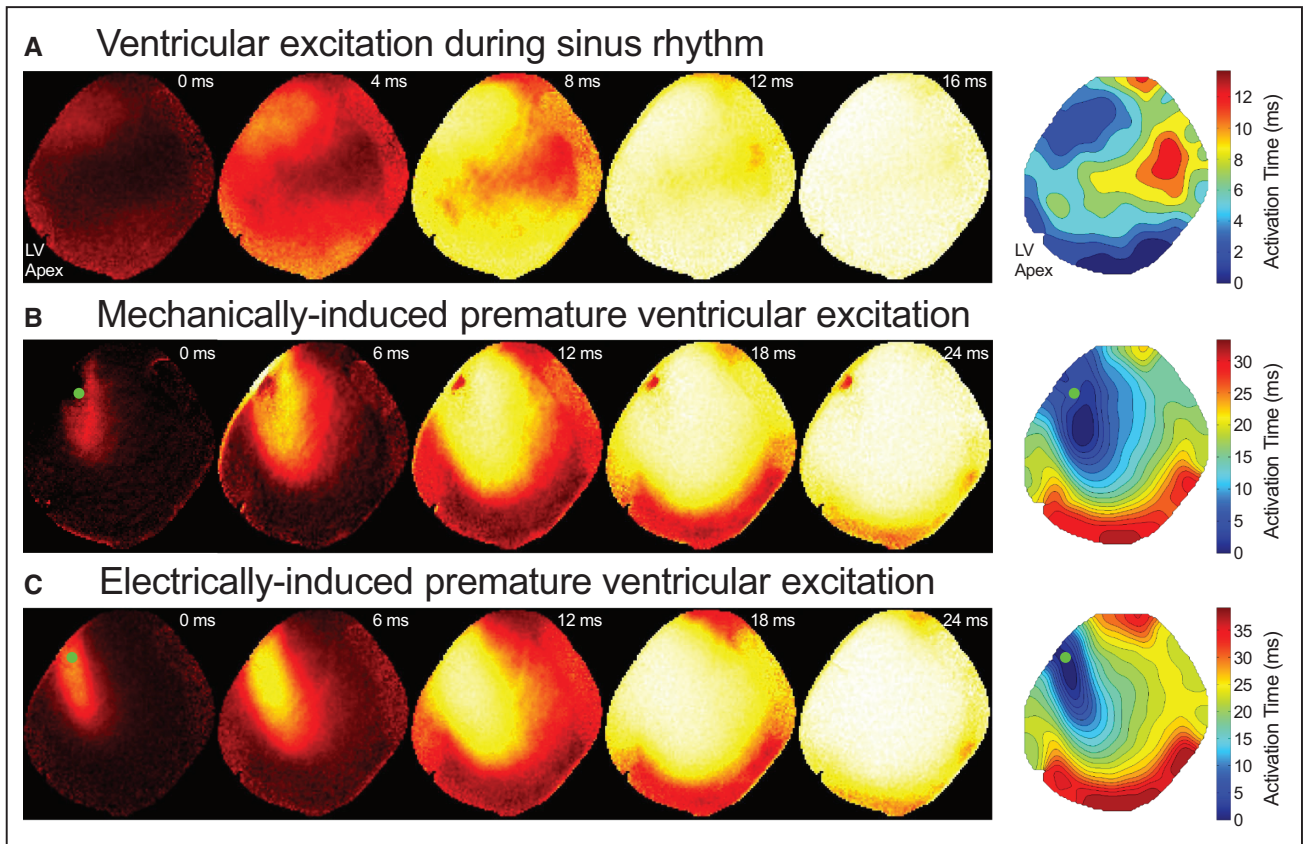
Figure 2. Left ventricular excitation visualized by epicardial optical mapping. Representative recordings during sinus rhythm (**A**) and mechanically (**B**) or electrically induced (**C**) excitation (from Movies II through IV in the Data Supplement) and maps of activation time (0 ms represents earliest epicardial activation in the associated map). Mechanical and electric stimulations were triggered at the same midlevel left ventricular (mid-LV) freewall location (green dots). Isochrones represent 2 ms steps. Note that the dark region at the mechanical stimulation location is an artifact caused by the probe entering the field of view, and the notch at the LV apex is caused by the surface ECG electrode.

Table. Comparison of Excitation Induced Mechanically or Electrically at the Same Site (Midlevel Left Ventricular Freewall)

Type of Stimulation	dV_m/dt_{max} (F_n/ms)	APD_{50} (ms)	APD_{90} (ms)	CV_{max} (cm/s)
Mechanical	75±11	136±12	163±8	98±21
Electric	71±8	134±11	164±10	92±27
P value	0.219	0.313	0.875	0.438

Measurements are averaged from 6 hearts, with 3 stimuli of each type at 3 different sites per heart. *P* values are for comparisons between mechanical and electric stimulation by Wilcoxon signed-rank test. APD_X indicates action potential duration at X% repolarization; CV_{max}, maximum conduction velocity; and dV_m/dt_{max}, maximum rate of transmembrane potential change (in nominal units of normalized fluorescence, F_n, per ms).

of mean rate of local tissue deformation, peak force, mean stress, and intraventricular pressure surge amplitude (n=7, m=405), suggesting that none of these parameters scale well with arrhythmogenicity. However, local tissue indentation, required for PVE_M induction, was similar across all groups (Figure 4).

Role of SAC_{NS} and K_{ATP} Channels

Application of *Grammostola spatulata* MechanoToxin-4 (500 nmol/L) reduced PVE_M inducibility in all preparations, on average by 62% (n=5, m=48/77 PVE_M inductions prevented). In contrast, streptomycin (≤500 µmol/L) had no effect on PVE_M inducibility (n=6, m=0/270 PVE_M prevented).

The K_{ATP} channel blocker glibenclamide (≤10 µmol/L) also had no effect on PVE_M inducibility (n=6, m=0/78 PVE_M prevented), but resulted in a ≈10% decrease in heart rate (from 138±10 to 125±13 beats per minute; *P*=0.031). This was associated with slowed repolarization (Figure II in the Data Supplement) and a 12% increase in refractory period for PVE_M (from 218±32 to 244±41 ms; *P*=0.031).

Electrophysiological Effects of Intraventricular Volume Pulses

Pressure surges, observed during epicardial mechanical stimulation (Figure 1B), were mimicked by the application of intraventricular volume bursts. Pressure surge amplitude

(r=0.904, P=1.07×10^{-7}; Figure 5A) and pressure rise time (r=0.723, P=0.008) increased linearly with the size of rapid intraventricular balloon volume change, while pressure fall time was not correlated with the change in balloon volume (r=0.428, P=0.166).

Diastolic pressure surges (all with confirmed lack of elevated creatine kinase activity), even if about an order of magnitude larger than those measured during PVE_M-inducing epicardial stimuli (101±27 versus 15±3 mm Hg, induced by volume bursts of 130 versus 20 µL, respectively), did not trigger a single PVE_M (Figure 5B; n=6, m=108). If applied during the ECG T wave, no change in repolarization pattern was observed (Figure 5C; n=6, m=108). In contrast, pressure surges of 178±21 mm Hg (induced by volume bursts of 200 µL) were needed to trigger excitation (Figure 5A).

Discussion

Summary of Principal Findings

PVE_M is induced reliably in diastole, using subcontusional local stimuli (≈0.5 mJ in isolated rabbit heart). While accompanied by intraventricular pressure surges (≈15 mm Hg), the origin of electric activation always coincides with the mechanical contact site (similar to repetitive local mechanical stimulation[35]). PVE_M induction is correlated with the degree of local tissue indentation, but not with indentation rate, force, stress, or intraventricular pressure surge amplitude, in keeping with earlier suggestions that mechanical deformation at the contact site is a key determinant for mechanoelectric signal transduction.[34] Underlying mechanisms involve SAC_{NS}, as PVE_M induction is reliably attenuated by the specific[36] SAC_{NS} blocker *Grammostola spatulata* MechanoToxin-4. The lack of streptomycin effects, which is an efficient SAC_{NS} blocker in vitro,[37] confirms results from a porcine model of CC[38] and is in keeping with earlier reports on the limited efficacy of streptomycin for acute SAC_{NS} block in native myocardium.[39] The mechanosensitive K_{ATP} channel blocker glibenclamide has no effect on PVE_M inducibility per se, but shifts PVE_M to later time points as a result of reduced sinus rate, delayed repolarization, and prolonged electric refractoriness. As a result, impacts applied early after the original refractory period, identified before drug application, can become ineffective.
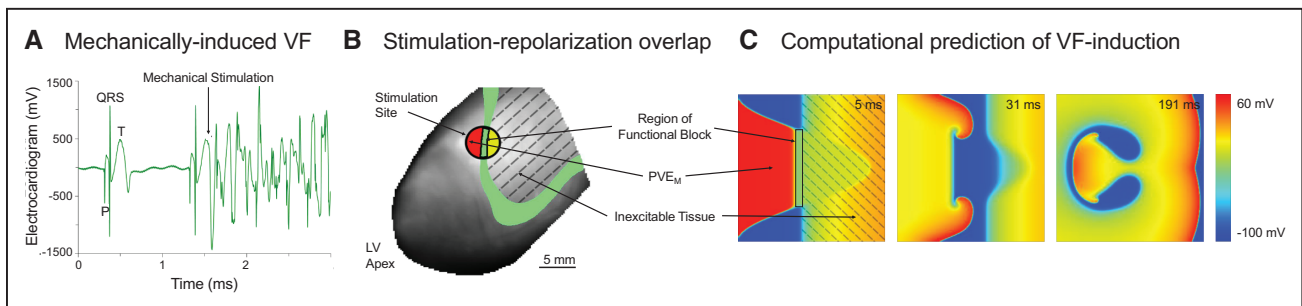

Figure 3. Mechanically induced ventricular fibrillation (VF). **A**, Surface ECG showing mechanical stimulation in early T wave, resulting in instantaneous VF (Movie V in the Data Supplement). **B**, Spatial interrelation of stimulation site and 50% repolarization isochrone (green). **C**, Comparison with previously published computational 2-dimensional modeling predictions,[27] showing mechanically induced premature ventricular excitation (PVE_M; red) arising directly adjacent to inexcitable tissue (yellow), forming a region of functional block (black rectangle) around which sustained reentry occurs. Adapted from Garny and Kohl[27] with permission of the publisher. Copyright © 2004, John Wiley and Sons. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
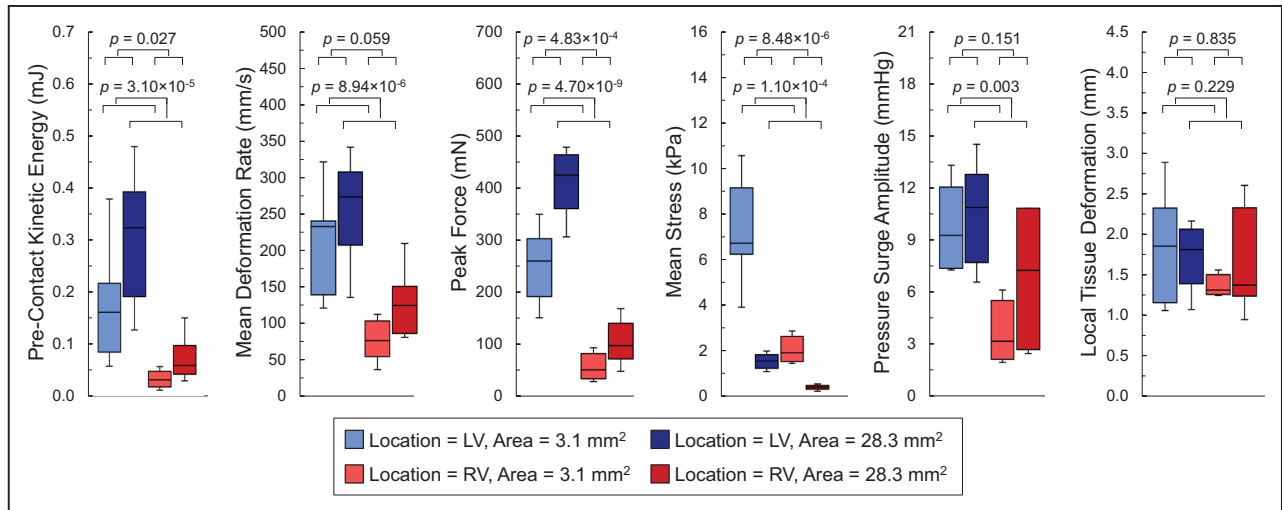
Figure 4. Mechanically induced premature ventricular excitation (PVE_M) thresholds. Box-and-whisker plots of mechanical stimulation characteristics (precontact kinetic energy, mean deformation rate, peak force, mean stress, intraventricular pressure surge amplitude, and local tissue deformation) at PVE_M threshold with varying combinations of freewall contact location (midleft ventricular [mid-LV; blues boxes] and midright ventricular freewall [mid-RV; red boxes]) and contact area (3.1 mm² [lighter boxes] and 28.3 mm² [darker boxes]). Only local tissue indentation (far **right**) forms a uniform predictor of PVE_M threshold across the various stimulation protocols. Measurements from 7 hearts. *P* values are for comparison of contact location and area by 2-way ANOVA with Tukey–Kramer post hoc tests.

With reduction of the coupling interval between preceding sinus activation and mechanical stimulation, PVE_M continues until stimulation timing enters the refractory period. If, and only if, repolarization is associated with a well-defined wave edge, PVE_M reliably and repeatably triggers VF. This occurs only if stimulation site and timing are such that PVE_M induction overlaps with the 50% repolarization isochrone of the preceding sinus beat.

In contrast, intraventricular pressure surges mimicking those seen during PVE_M-inducing epicardial stimuli do not result in a single occurrence of PVE_M, nor in noticeable changes in repolarization, even if increased in amplitude by an order of magnitude.

Taken together, these results suggest that ventricular excitation upon local mechanical stimulation is a result of SAC_{NS} activation, caused by local tissue deformation. The presence of a well-delineated trailing repolarization wave, and spatiotemporal colocalization of mechanically affected tissue with the trailing edge of the preceding wave, are preconditions for VF induction. The vulnerable window for CC-induced VF is thus defined in both time and space, explaining the short period during which mechanical stimuli can induce reentry for any given contact location, and why mechanically induced VF is so rare in real life. Our findings may have future implications for predictive assessment of individual athletes' CC risk (a target which until now has been lacking[40]), through measurement of ventricular repolarization patterns using noninvasive imaging techniques, such as electrocardiographic imaging[41] or overall dispersion of repolarization by the T-peak to T-end interval[42] (whose prolongation has been shown to be an independent risk marker for sudden cardiac death[43]).

Mechanisms of PVE_M Induction

Previously reported PVE_M induction by transiently increased intraventricular volume in isolated hearts[11,44–46] occurred in different studies at remarkably similar pulse volumes (which define tissue stretch; eg, 750 μL pulses resulted in near 100% PVE_M occurrence in hearts isolated from ≈2 kg rabbits[11]). However, associated changes in intraventricular pressure (a function of the interaction between volume pulse dynamics and tissue viscoelastic properties[47]) show high variability.[45] In addition, where seen, ventricular excitation on volume loading is focal, often originating in the posterolateral LV,[11] the most compliant region where tissue distension is likely to be largest.

This suggests that stretch of (part of the) myocardium is a primary determinant of electrophysiological responses to mechanical stimulation. Our results support this view, as the threshold for PVE_M, regardless of contact location (LV, RV) and area (3.1 and 28.3 mm²), correlates with local tissue deformation only (indentation depth). In our hands, independently applied intraventricular pressure surges up to an order of magnitude larger than those seen with epicardial stimulation do not result in PVE_M. Note that pressure surges in our study were achieved by rapid application of comparatively small volume pulses (20–130 μL), using active balloon inflation and deflation to mimic more closely the CC setting, where pressure surges (1) are exceedingly short lived and (2) arise without intraventricular volume increase.

Our results also identify SAC_{NS} as a key contributor to PVE_M, as application of *Grammostola spatulata* MechanoToxin-4 reduces its inducibility. This role of SAC_{NS} in depolarizing cells to threshold during mechanical stimulation is further reflected by the lack of an additional delay between mechanical stimulation and the onset of electric excitation when the coupling interval is reduced (as SAC_{NS} are not inactivated by normal AP dynamics).

Although mechanisms by which external energy delivery give rise to ectopy are clearly different for mechanical and electric stimulation, our results confirm that, once excitation and ventricular activation occur, their downstream characteristics are similar, as previously shown in open-chest, anesthetized
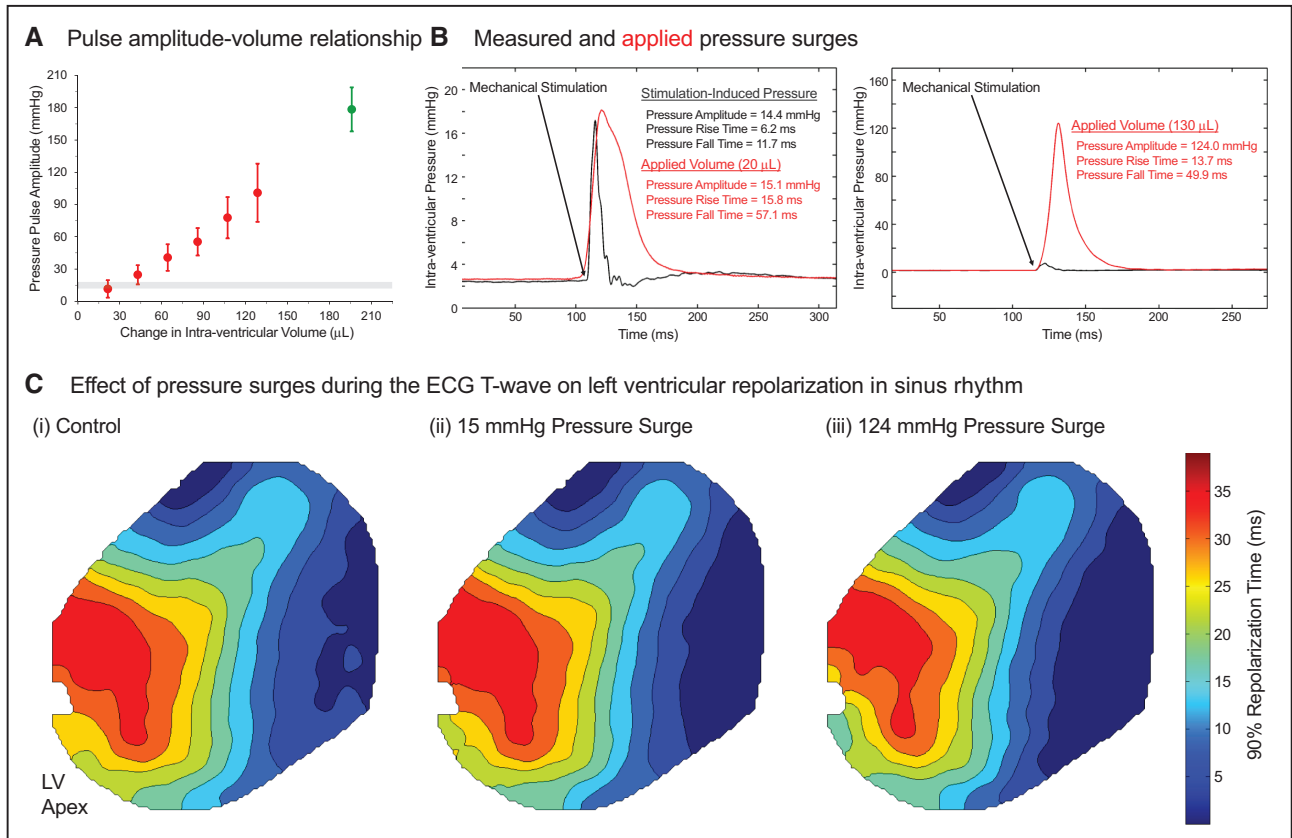
Figure 5. Intraventricular volume pulses. **A,** Relationship between intraventricular balloon volume pulse and peak pressure, averaged from 6 hearts. Red points indicate volumes assessed in the standard experiments (which were not associated with elevated creatine kinase release; Figure III in the Data Supplement), whereas a mechanically induced premature ventricular excitation (PVE$_M$)–inducing excessive volume pulse (200 µL) is shown in green. The gray horizontal band indicates the range of pressure amplitudes measured during PVE$_M$-inducing epicardial mechanical stimulation. **B,** Representative pressure surges measured during epicardial mechanical stimulation (black) and with active injection/retraction of 20 µL (**left**) or 130 µL (**right**) intraventricular volume pulses (red). **C,** Representative optical mapping data for 90% repolarization time (0 ms represents earliest repolarization in the associated map) in sinus rhythm during (i) control and application of (ii) 15 mm Hg or (iii) 124 mm Hg pressure surges (using stimuli shown in **B**) applied at the peak of the T wave. Isochrones represent 5 ms steps. Note that the notch at the left ventricular (LV) apex is caused by the surface ECG electrode in the field of view.

dogs[48] and rat isolated hearts (in which similar downstream calcium dynamics were also seen).[33] Electric stimulation initially excites a narrower tissue region than mechanical stimulation (elongated in the locally prevailing cell direction; compare early activation isochrones in Figure 2B and 2C and Movies III and IV in the Data Supplement), as local electric stimulation affects a smaller tissue region (contact area of the stimulation electrode was one-hundredth that of the mechanical probe, 0.031 versus 3.1 mm²).

Mechanisms of VF Induction

In the porcine model of CC, a critical determinant of electrophysiological outcome is precordial impact timing relative to the ECG.[8,24,25] Impacts just before the T-wave peak can induce VF, whereas impacts at other stages of the cardiac cycle result in different transient rhythm disturbances.[49] The vulnerable time window for precordial impact-induced VF in pig is short: ≈15 ms,[49] compared to ≥100 ms for extracorporeal electric stimulation in other large animals (dogs).[50] In smaller hearts, vulnerable windows are narrower: we could not trigger VF if impact timing varied by ±5 ms, whereas the electric vulnerable window in rabbit is ≈20 to 25 ms.[51]

A pig model of CC also highlighted a correlation of VF inducibility with the amplitude of impact-induced intraventricular pressure surges, suggesting that the rapid pressure increase may be causal for electric effects.[29] Furthermore, block of mechanosensitive K$_{ATP}$ channels by glibenclamide reduced VF occurrence.[22] This observation motivated the hypothesis that CC-induced VF represents an acquired form of abnormal repolarization.[8,24]

The role of intraventricular pressure surges is supported by experiments with acute LV balloon inflation in rabbit isolated hearts.[44] Pressure surges of >200 mm Hg, caused by volume injections of 800 to 1600 µL (a ≈80%–160% increase in intraventricular volume; no assessment of tissue integrity reported) result in increased dispersion of repolarization and, occasionally, VF (11% of volume pulses), in an amplitude/timing-dependent manner. In our hands, using hearts of similar size, intraventricular volume increases >500 µL cause structural damage (assessed by creatine kinase release; Figure III in the Data Supplement). In contrast, the exceedingly short-lived pressure surges during CC occur in the absence of a rise in intraventricular volume. Given that tissue viscoelasticity dampens the translation of mechanical stress into stretch, it is likely that

CC-induced pressure surges cause little, if any, tissue distension beyond what is induced locally by precordial impact. In keeping with this suggestion, excitation in the in situ pig heart during CC-inducing impacts is focal and originates from tissue immediately underneath the extracorporeal impact site.[52]

In the present study, rapid infusion and active retraction of 20 μL into the LV balloon result in pressure surges similar in amplitude to those seen during PVE_M, albeit with slightly slower dynamics (as expected from an intervention that is not isovolumic per se). Increasing volume pulses up to 130 μL (≈10%–15% of LV volume) gives rise to pressure surges up to an order of magnitude larger than those during PVE_M-inducing stimulation, but still does not result in excitation or marked changes in repolarization (volumes exceeding ≈200 μL are needed to trigger PVE_M in diastole; Figure 5A). This suggests that precordial impact-induced pressure surges are not the main driver of mechanical VF induction, but a covariate of impact severity.

Of course, it is possible that pressure surges have effects on repolarization in whole animals that are not preserved in isolated hearts, in particular if they involve nervous system responses. Given that CC-induced VF is near instantaneous and that mechanically induced changes in cardiac electrophysiology persist in situ after surgical and pharmacological denervation,[53] it remains unlikely that these would be major determinants of electrophysiological outcomes.

In terms of possible roles of K_{ATP} channels in CC-induced VF, it is noteworthy that under conditions of normal oxygen supply, K_{ATP} channels are inactivated[54] and not responsive to mechanical stimulation.[19,21,55] In our experiments, application of the K_{ATP} channel blocker glibenclamide has no effect on PVE_M inducibility, which is in agreement with previous reports from anesthetized pigs.[22] We observe a glibenclamide-induced slowing of sinus rate, delayed repolarization, and an increase (by ≈25 ms) in refractory period for PVE_M. This is in keeping with nonspecific effects reported for glibenclamide.[56,57] The observed changes in repolarization timing and refractoriness exceed the narrow vulnerable time window for VF inducibility. Therefore, glibenclamide application may shift vulnerability for mechanical VF induction past critical timings, identified in control conditions. This could explain the previously reported reduction in VF occurrence during precordial impact with glibenclamide in the pig, where impact timings that previously induced VF failed after drug application.[22]

In contrast to the view that mechanically induced VF arises primarily out of repolarization abnormalities, 2-dimensional[27] and 3-dimensional[28] computational modeling, including representations of SAC_{NS}, suggests that CC-induced reentry is a consequence primarily of abnormal excitation. In particular, if a mechanical stimulus overlaps the trailing edge of the normal repolarization wave, it can induce VF by causing PVE_M in tissue that has regained excitability (ie, where V_m levels are below SAC_{NS} reversal potential), while at the same time not only increasing electrophysiological heterogeneity by regional AP shortening in tissue that is still excited (ie, where V_m levels are above SAC_{NS} reversal potential) but, crucially, by forming a region of functional conduction block at the intersection of the normal repolarization wave edge and the PVE_M-induced excitation. Our results support this prediction.

In all cases where epicardial stimulation resulted in VF, the mechanically affected tissue overlapped with the 50% repolarization isochrone, traversing the epicardial surface. The vulnerable time window for CC-induced VF is therefore location specific, existing both in time and in space.

Limitations

The key limitation is the low incidence of local mechanical stimulation-induced VF (n=3/32 animals, 9%), which prevented a more systematic assessment of the vulnerable window. This incidence is in keeping, however, with the exquisite dependence of VF induction on repolarization dynamics, stimulation site, and stimulation timing, whose conditions will be met only rarely, in hearts that display a specifically well-delineated repolarization wave. The necessary conditions occurred in a small subset of hearts only, because of intersubject variability, but in hearts that fulfilled the preconditions, VF was reliably induced. The low incidence of VF in our study is in line with the rarity of CC-induced VF in humans[8] and the individual susceptibility in the present gold standard in vivo model of CC.[58] In addition, in physiological conditions, Langendorff-perfused rabbit hearts show an exceedingly low probability of VF induction also using electric stimulation.[59] This could be further compounded by a reduction in arrhythmia susceptibility by blebbistatin,[60] suggesting that our observations form a conservative estimate.

Conclusions

Our findings demonstrate that local subcontusional mechanical stimuli can reliably trigger PVE_M, originating at the probe–tissue contact site, and require SAC_{NS}, whose activation scales with the degree of local tissue deformation. PVE_M cause VF if, and only if, there is overlap of mechanical stimulation with the trailing edge of the preceding repolarization wave. As a result, there is a subject-specific set of vulnerable windows for CC-induced VF both in time and in space.

Disclosures

None.

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