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## TRANSLATIONAL PHYSIOLOGY |

# Stretch-induced ventricular arrhythmias during acute ischemia and reperfusion

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**Parker, Kevin Kit, James A. Lavelle, L. Katherine Taylor, Zifa Wang, and David E. Hansen.** Stretch-induced ventricular arrhythmias during acute ischemia and reperfusion. *J Appl Physiol* 97: 377–383, 2004; 10.1152/jappphysiol.01235.2001.—Mechanical stretch has been demonstrated to have electrophysiological effects on cardiac muscle, including alteration of the probability of excitation, alteration of the action potential waveform, and stretch-induced arrhythmia (SIA). We demonstrate that regional ventricular ischemia due to coronary artery occlusion increases arrhythmogenic effects of transient diastolic stretch, whereas globally ischemic hearts showed no such increase. We tested our hypothesis that, during phase Ia ischemia, regionally ischemic hearts may be more susceptible to triggered arrhythmogenesis due to transient diastolic stretch. During the first 20 min of regional ischemia, the probability of eliciting a ventricular SIA ( $P_{SIA}$ ) by transient diastolic stretch increased significantly. However, after 30 min,  $P_{SIA}$  decreased to a value comparable with baseline measurements, as expected during phase Ib, where most ventricular arrhythmias are of reentrant mechanisms. We also suggest that mechano-electrical coupling may contribute to the nonreentrant mechanisms underlying reperfusion-induced arrhythmia. When coronary artery occlusion was relieved after 30 min of ischemia, we observed an increase in  $P_{SIA}$  and the maintenance of this elevated level throughout 20 min of reperfusion. We conclude that mechano-electrical coupling may underlie triggered arrhythmogenesis during phase Ia ischemia and reperfusion.

ventricular; Langendorff; myocardial infarction; mechano-electric signaling

VENTRICULAR ARRHYTHMIAS ACCOMPANYING an arrest of myocardial perfusion are the primary cause of death in the majority of fatalities associated with myocardial infarction and are a major provocation of sudden cardiac death (50). The role of acute myocardial ischemia in fatal arrhythmias has been studied (10, 38–40, 44) and attributed to the alteration in electrical properties of ventricular tissue, affecting excitability and conduction of the action potential (23, 46, 63). These interruptions in normal electrical function of the myocyte are the result of altered membrane ionic currents and their diastolic concentrations in both the intra- and extracellular spaces (43, 63). Arrhythmias associated with ischemia are generally classified as phase I (during the first 30 min), phase II (between 5 and 72 h), and phase III (chronic stage after infarct). Phase I arrhythmias are further subdivided into Ia and Ib, where Ia arrhythmias occur during the first 10 min of ischemia and are

due to both reentrant and triggered mechanisms and Ib arrhythmias occur between 20 and 30 min of ischemia and are of reentrant means. Reperfusion-induced arrhythmias after ischemic episodes are attributed primarily to triggered mechanisms.

Triggered arrhythmias are characterized by an external stimulus, primarily classified as early afterdepolarizations or afterdepolarizations. In studies directed toward understanding the role of mechano-electrical coupling in arrhythmogenesis, early afterdepolarizations have been associated with increased stretch conductance in computer simulations (43) and in mechanically induced ectopic beats in experimental studies (13). Myocardial stretch during the action potential has been observed to alter the action potential duration (19, 20, 22, 24), whereas transient diastolic stretch has been shown to result in depolarization (36), often sufficient to elicit an action potential (13, 24). Mechanical stretch has been demonstrated to generate atrial and ventricular arrhythmias (14, 17, 41, 51).

Regional inhomogeneities in contractility and mechanical restitution may serve as foci for stretch-induced arrhythmias (SIAs). These inhomogeneities can be attributed to localized ischemia (12, 42) or hypertrophy localized to various regions on the ventricular free wall and septum (11). Such inhomogeneities will result in abnormal distributions of strain in the ventricular wall. The presence of abnormalities in left ventricular (LV) wall motion has been correlated with the incidence of cardiac arrhythmias (6, 31) and sudden cardiac death among patients with coronary artery disease (6). We hypothesize that this dyskinesia will perturb membrane conductivities with the potential to display altered kinetics during mechanical perturbation (15, 32, 58), potentiating an increase in SIAs.

We tested the hypothesis that regional ischemia is more conducive than global ischemia to ventricular SIAs and from these results developed an ischemic heart model to test our hypothesis that mechanical stretch may underlie phase Ia and reperfusion ventricular arrhythmias. Furthermore, we hypothesized that regionally ischemic hearts would not be as susceptible to SIAs during phase Ib, when reentrant arrhythmogenesis is observed. We found that the probability of eliciting an SIA is higher during regional ischemia than during global ischemia even when contractile capabilities are comparable. Furthermore, we observed that the incidence of SIAs throughout 20 min of regional ischemia and 30 min of reperfusion matched previously reported profiles for triggered arrhythmias. In the

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phase Ib time period during which reentrant mechanisms are exclusively reported (38), our results show a decreased vulnerability to mechanically triggered ventricular arrhythmias.

## METHODS

**Langendorf-perfused heart.** The Langendorf perfusion system and stretch protocols have been previously reported (35). Briefly, hearts were harvested from male New Zealand White rabbits that were anesthetized with pentobarbital sodium (60 mg/kg) mixed with heparin (1,000 U). The heart was then attached to and perfused by a Langendorf apparatus via the aorta. The heart was submerged in perfusate while the atria were opened and leaflets of the mitral and tricuspid valves detached. A plastic ring was sutured into the mitral annulus to secure the ventricle to the conduit. The atrioventricular node was surgically ablated. A fluid-filled latex balloon was threaded through the ring and into the LV. A micromanometer-tipped catheter (model SPC-330A, Millar, Houston, TX) within the balloon measured instantaneous LV pressure. The monophasic action potential (MAP) was recorded and monitored in real time from an electrode placed on the LV epicardial surface, away from regionally ischemic regions (model 200, EP Technologies, Sunnyvale, CA). Wire pacing electrodes were placed on the epicardial surface of the LV apex and right ventricle and paced the heart at 2 Hz.

The isotonic perfusate consisted of 120 mM NaCl, 5.0 mM KCl, 20 mM sodium acetate, 1.2 mM MgCl<sub>2</sub>, 5.0 mM HEPES, 1.5 mM CaCl<sub>2</sub>, 10 mM glucose, 0.3 mM probenecid, and 0.05 mM NaOH. After filtration (0.45 μm), 1% neonatal calf serum was added. The solution was bubbled with 100% O<sub>2</sub>, and the pH was maintained at ~7.4. Coronary perfusion pressure (CPP) was maintained between 70 and 80 mmHg throughout the experiment and checked periodically.

The volume pump consists of a hydraulic piston driven by a stepper motor apparatus (Compumotor Indexer model AT 6400, microstepping drive model S6, and Linear Motor Platen model PO-L20-P18, Parker Compumotor, Rohnert Park, CA). A resistive linear variable displacement transducer (DRC model LX1A-0004-BE-L10, Parker Compumotor) determined the position of the piston. The output of the linear variable displacement transducer was calibrated to measure absolute balloon volume (linearity within 1%) and was digitized at 1 kHz by a digital computer (model 486-DX4-66, Gateway 2000, North Sioux City, SD) using a 12-bit analog-to-digital converter (LabMaster TM-100, Scientific Solutions, Solon, OH). The MAP, LV pressure, the rate of rise of the LV pressure, LV volume, and coronary perfusion pressure were amplified and continuously digitized during each experimental stage at 1 kHz by the LabMaster TM-100 analog-to-digital board and stored at 500 Hz on the computer's hard disk for subsequent data analysis.

**Experimental protocols.** Between stretch protocols, isovolumic measurements were taken to monitor ventricular mechanics. The LV stretch protocol (stretch) consisted of 20 iterations of a control-stretch cycle where each cycle was composed of eight pacing beats followed by a quiescent pacing period to exclude intrinsic ectopia. Pacing was then resumed and continued for 4 s (8 beats) before a transient diastolic stretch was delivered by precise increase of the LV balloon volume (ΔV), followed by a return to the initial steady-state volume. During stretch, no pacing signals were delivered to the heart. From the 20 cycles, a probability of ventricular SIA ( $P_{SIA}$ ) was computed at each ΔV such that a  $P_{SIA}$  vs. ΔV curve was established at baseline condition (nonischemic). A value from this sigmoidal curve corresponding to a 50%  $P_{SIA}$  value was chosen and tested at intervals throughout the experiment.

To induce global ischemia ( $n = 6$ ), perfusion pressure was reduced from 80 to 40 mmHg. Regional ischemia ( $n = 9$ ) was induced by ligation of the left circumflex. Reperfusion of the ischemic region occurred after 30 min of ischemia by release of the ligature. Control, or mock ischemia, experiments ( $n = 6$ ) were conducted where a suture was placed around the left circumflex but not tied. Data are reported as means ± SE. Trends in each parameter with time were assessed by one-way ANOVA using Analyse-it 1.70 (Analyse-it

Software, Leeds, UK). If the overall trend with time was significant, values of  $P_{SIA}$ , maximum systolic pressure ( $P_{max}$ ), and end-diastolic pressure ( $P_{ed}$ ) were each compared with baseline using Bonferroni's correction for multiple comparisons. Single comparisons of  $P_{SIA}$ ,  $P_{max}$ , and  $P_{ed}$  in hearts that were globally or regionally ischemic for 5 min vs. their baseline values were made with Student's *t*-test for paired samples. A value of  $P < 0.05$  was considered significant for all tests.

## RESULTS

Figure 1 shows examples of ventricular SIAs. Rapid change in LV volume may induce ventricular tachycardia (Fig. 1A). We often observe nonsustained ventricular tachycardia in our experimental preparation. When the stretch trigger is of sufficient magnitude and velocity, ventricular fibrillation can occur as depicted in Fig. 1B. In the present study protocol, high grades of ventricular ectopy were intentionally avoided when stretching, so as to prevent unnecessary degradation of the heart during the long experiments. A single or pair of premature ventricular contractions was typically elicited by a transient ventricular stretch that resulted in intraventricular pressures of ~80 mmHg, as previously reported (35).

**Arrhythmogenic mechanoelectrical coupling during regional and global ischemia.** In chronically ischemic hearts, the incidence of arrhythmias accompanies the deterioration in mechanical function. However, in acute ischemia, we hypothesized that this would not always be the case. Recent theoretical calculations (25, 45) indicate that the inhomogeneity in contractility in the vicinity of the infarct would facilitate the development of localized regions of stretch that might serve as mechanoarrhythmogenic foci. This is in contrast to the globally ischemic heart, whose contractility is reduced in a relatively uniform manner.

In Fig. 2A, we show  $P_{max}$ , an indicator of ventricular contractility, and  $P_{ed}$ , a measure of ventricular compliance, as a function of time for ischemic and mock ischemic hearts during ischemia and reperfusion. During 5 min of regional no-flow ischemia, a statistically significant decrease in  $P_{max}$  is observed ( $P = 0.002$ ). A statistically significant decrease in  $P_{max}$  is also observed among hearts with 5 min of low-flow, global ischemia ( $P = 0.014$ ). No statistically significant decrease in  $P_{max}$  or  $P_{ed}$  was observed for control hearts. After 5 min of their respective ischemic conditions, hearts of both modalities showed similar contractility, as indicated by mean  $P_{max}$  values. Figure 2B depicts the observed changes in  $P_{SIA}$  from preischemic to ischemic values. For mock ischemic and globally ischemic hearts, no statistically significant change was seen in  $P_{SIA}$  over 5 min. Regionally ischemic hearts showed an increase in  $P_{SIA}$  ( $P = 0.010$ ) consistent with our hypothesis. That the overall contractility of both global and regionally ischemic hearts was comparable while regionally ischemic hearts were more susceptible to SIAs suggests that metabolically induced contractile dysfunction alone is not necessarily mechanoarrhythmogenic. The data indicate that an inhomogeneity may facilitate mechanical arrhythmogenesis and that common indicators of contractility may not elucidate the complex mechanical dysfunction underlying arrhythmogenic mechanoelectrical signaling.

**Arrhythmogenic mechanoelectrical coupling during regional ischemia and reperfusion.** We then asked whether the  $P_{SIA}$  profile during acute ischemia and reperfusion would appear similar to the arrhythmogenesis previously reported

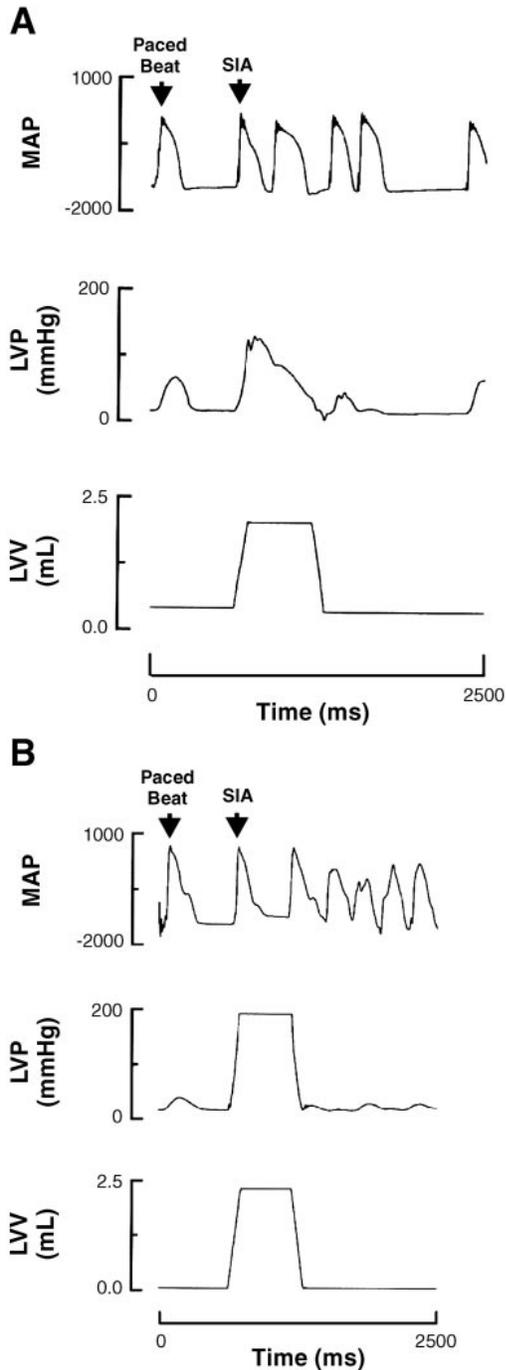


Fig. 1. Stretched-induced arrhythmias (SIA). *A*: stretch-induced ventricular tachycardia. *B*: stretch-induced ventricular fibrillation. MAP, monophasic action potential; LVP, left ventricular pressure; LVV, left ventricular volume.

(49). We induced regional ischemia by coronary artery ligation for 30 min and then released the suture, reperusing the ischemic region. The hemodynamic effects of acute coronary artery occlusion and reperfusion are shown in Fig. 3. In the figure, time course of the experiment and the changes in diastolic and systolic pressures, as well as the change in  $P_{SIA}$ , during ischemia and reperfusion are depicted. In Fig. 3*A*, the immediate loss of  $P_{max}$  after coronary artery occlusion is observed, but it is recovered during reperfusion where contractility recovers to levels comparable with mock ischemic hearts.

Mock ischemic hearts show a gradual, but statistically insignificant, degradation of  $P_{max}$  during Langendorff perfusion (ANOVA,  $P = 0.29$ ).  $P_{ed}$  values were unchanged for ischemic (ANOVA,  $P = 0.79$ ) and mock ischemic hearts (ANOVA,  $P = 0.93$ ). Thus LV compliance was relatively constant throughout our experiments, whereas LV contractility was reduced during ischemia and restored during reperfusion.

The mechanoarrhythmogenic effects of ischemia and reperfusion are summarized in Fig. 3*B*. In the figure, the mean  $P_{SIA}$  is plotted as a function of time and the onset and duration of coronary artery occlusion and reperfusion are indicated. A 25% ( $P < 0.05$ ) increase in  $P_{SIA}$  was observed 5 min after the onset of ischemia. Twenty minutes after the onset of ischemia,  $P_{SIA}$  had continued to increase an additional 30% ( $P < 0.05$ ) over baseline; however, this time point is at the transitional period when phase Ib arrhythmias are most often observed (21) and cell-to-cell electrical uncoupling begins (49). Previous studies showing disruption of gap junction conductivity during transient ischemia suggest that electrical isolation of the infarct

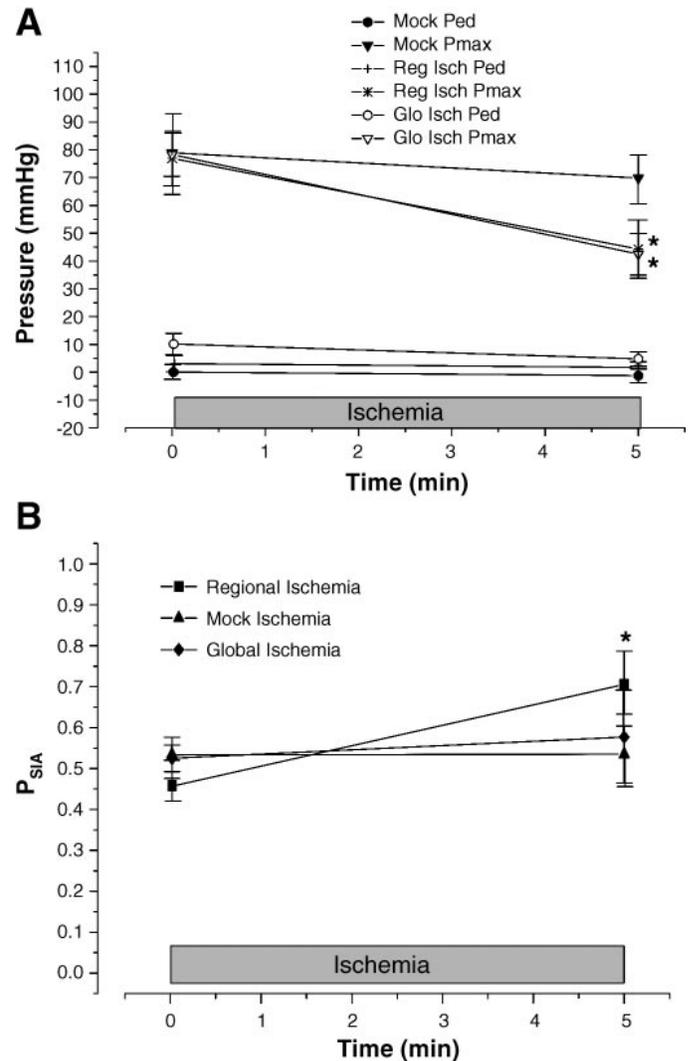


Fig. 2. Global ischemic vs. regional ventricular ischemia. *A*: maximum systolic pressure ( $P_{max}$ ) and end-diastolic pressure ( $P_{ed}$ ) during 5 min of acute ischemia. Reg, regional; Isch, ischemia. *B*: probability of ventricular SIA ( $P_{SIA}$ ) during acute ischemia. \* $P < 0.05$ .

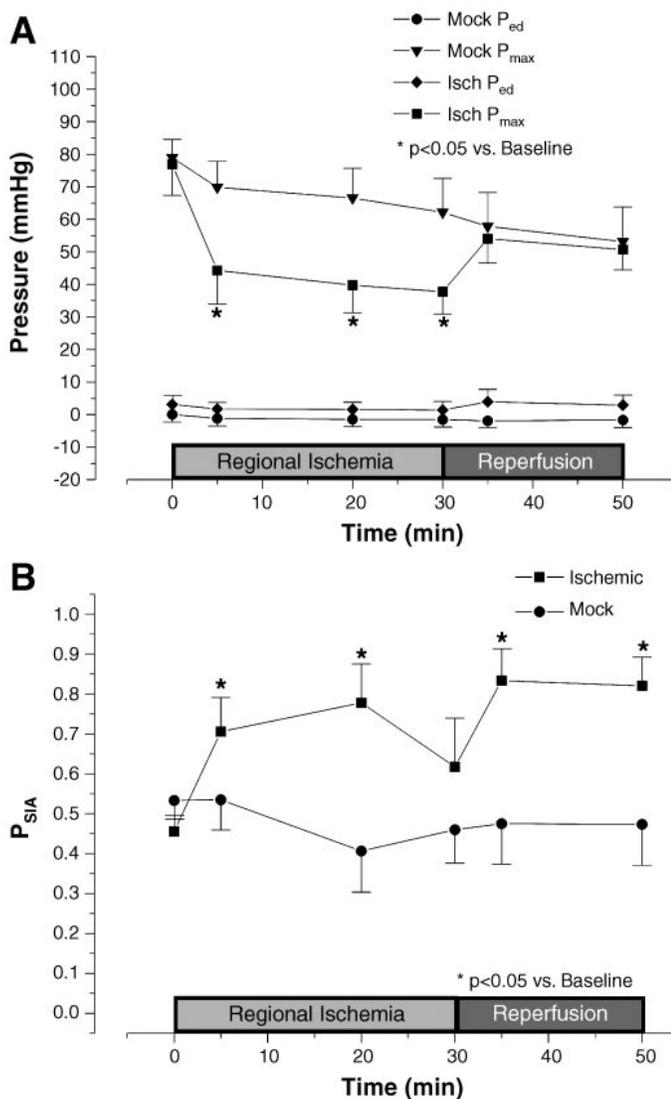


Fig. 3. Hemodynamic and arrhythmogenic response to acute regional ischemia and reperfusion. *A*:  $P_{max}$  and  $P_{ed}$ . *B*:  $P_{SIA}$ .

would occur at a time  $>20$  min after coronary artery occlusion (49). After 30 min, the mean value of  $P_{SIA}$  had fallen to a level that was not statistically significant vs. baseline levels ( $P > 0.05$ ). We attribute this decrease to electrical uncoupling of the ischemic region from perfused regions, thus isolating regions within the infarct that might have increased sensitivity to arrhythmogenic stimuli such as stretch. For a SIA to occur, a critical volume of tissue must be depolarized to threshold and a conduction pathway from this tissue must exist. We hypothesize that electrical uncoupling prevents the development of stretch-induced action potentials originating within the infarct.

Five minutes after release of the ligature constricting the left circumflex,  $P_{SIA}$  increases substantially, exceeding values observed during ischemia, with nearly a 40% increase over preischemic values ( $P < 0.05$ ). This occurs at the same time that  $P_{max}$  returns to values comparable to that of mock ischemic hearts. Thus, even though contractile capability is restored,  $P_{SIA}$  increases substantially. The increase in  $P_{SIA}$  during the first 5 min of ischemia and after 5 min of reperfusion is illustrated in Fig. 4, which shows typical MAP recordings during an experiment.

Twenty consecutive stretch sequences before ligation of the left circumflex artery, 5 min after ligation, and 5 min into reperfusion are depicted. Single ventricular extrasystoles, ventricular pairs, and nonsustained ventricular tachycardia are observed as the  $P_{SIA}$  increases from 0.50 before ischemia, to 0.80 during ischemia, and then to 1.00 during reperfusion. When extrasystoles and ventricular pairs occurred after stretch, they were excluded from consideration because they were probably ventricular escape beats.  $P_{SIA}$  remained higher than any value measured during ischemia throughout the observed period of reperfusion ( $P < 0.05$  at 20 min) even while the value of  $P_{max}$  is similar to that measured in control experiments where no such increase in  $P_{SIA}$  is observed. Thus it would appear that the restoration of contractility within the infarcted region is not sufficient to reduce the risk of SIA.

#### DISCUSSION

Regional ischemia facilitates stretch-induced arrhythmias. Our data suggest that arrhythmogenic events potentiated by transient LV dilatation during ischemia are sensitive to the geometry of the ischemic region. Although global ischemia may exacerbate the normal regional differences in diastolic and systolic function, the gradients in electrical and mechanical function are not as locally concentrated as observed during regional ischemia, where such differences may occur with a spatial dispersion on the scale of cell lengths.

Ischemic ventricular myocardium has been shown to be less contractile than normal surrounding myocardium (1, 29). Within minutes of acute myocardial ischemia, paradoxical holosystolic lengthening is observed (54). This lengthening is attributed to the reduced rate and magnitude of tension development with respect to noninfarcted regions against which it

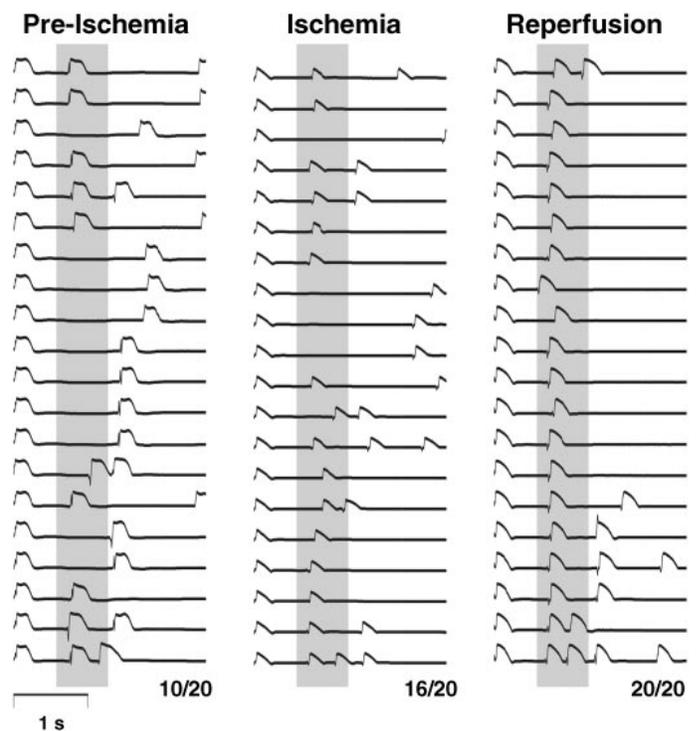


Fig. 4. Twenty monophasic waveforms recorded during a typical experiment. Recordings were made at baseline (preischemia), after 5 min of regional ischemia (ischemia), and after 5 min of reperfusion (reperfusion). Vertical shaded bars indicate timing of left ventricular volume increase (stretch).

contracts. Experimental preparations of weak and strong myocardial tissue in series demonstrate paradoxical lengthening of weaker regions (61). This has also been demonstrated by segment length measurements during regional ischemia of intact hearts (27). Previously, the contractile and restitutive heterogeneity induced by regional ischemia was shown to alter ventricular wall mechanics and has been correlated with the incidence of arrhythmias (6, 8, 31, 62) and sudden cardiac death (7, 48, 53, 60). In patients diagnosed with LV infarcts, regions of anomalous deformation were noted during magnetic resonance imaging tagging studies (28) and were attributed to stretch. An early report also noted asynchronous contraction and relaxation of ischemic regions compared with well-perfused, surrounding myocardium (56). These reports support the conclusion that inhomogeneities in activation and contractility, such as those induced by ischemia, may contribute to the development of stretch-induced arrhythmogenic foci.

Although the above-mentioned studies refer to systolic stretch, the regional heterogeneities induced by acute ischemia will also affect diastolic distensibility (26). Theoretical calculations (25, 45) predict eccentric strain patterns in the ischemic border region and in outlying regions of the infarct during diastolic filling that are not present during global ischemia. The spatial patterning of strain was reported to be similar during both systole and transient diastolic stretch. These regions of eccentric strain may serve as foci for mechanoarrhythmogenic events. These reports focus on the inhomogeneity presented by localized ischemia, and others have focused on the regional inhomogeneities presented by dilatation (11). However, should localized regions of hypertrophy or scarring be present in the intact ventricle, the hypothesis may extend to the mechanical abnormalities that these conditions present as well.

*Mechanoelectrical coupling potentiates phase Ia arrhythmias.* The results of this study indicate that regionally ischemic hearts are more vulnerable to ventricular SIAs during the time period associated with phase Ia arrhythmias than that period corresponding to phase Ib arrhythmias. Previous reports in the literature foreshadow this finding because Ia arrhythmias have been correlated to both reentrant and triggered mechanisms (39, 40), whereas Ib arrhythmias are correlated exclusively to reentrant means (38). The inability to mechanically induce arrhythmias above baseline during phase Ib implies that, at a certain point during acute ischemia, vulnerability to arrhythmogenic mechanoelectrical coupling is reduced.

Disruption of gap junctions after >20 min of ischemia serves to electrically uncouple ischemic and perfused regions of the heart (49). Our choice of the rabbit as an experimental model was due in part to their lack of coronary collaterals (2, 3, 30). Thus a relatively strict demarcation of the ischemic region is achieved after gap junction closure. Before the present study, we confirmed this in our Langendorff-perfused rabbit heart preparation during optical imaging studies with voltage-sensitive dyes. Thus, when the infarct is electrically isolated, the continuing loss of ionic homeostasis and ultrastructural integrity is prevented from contributing to triggered action potentials propagating from within the ischemic region.

*Mechanoelectrical coupling potentiates reperfusion-induced arrhythmias.* On release of the coronary artery blockade, we observed a rapid increase in the  $P_{SIA}$  to levels superseding what was observed in the earliest moments of ischemia. This increase in arrhythmias was accompanied by a restoration of

contractile function. Our data suggest that some of the attributes of acute ischemia and reperfusion, including increased cytosolic calcium and hypercontracture associated with reoxygenation of the tissue, contribute to the heart's increased vulnerability to mechanoarrhythmogenic stimuli.

Two factors are credited with facilitating reperfusion arrhythmias: cytosolic calcium overload (34) and oxygen-derived free radicals (4). Both factors may act synergistically (18, 33), or calcium overload alone may facilitate the development of early ventricular arrhythmias (9, 18, 34). Increased levels of cytosolic calcium may increase the responsiveness of myocardial tissue to stretch. However, another potential factor in the increased susceptibility of reperfused hearts to arrhythmia may be the effects of hypercontracture and associated ultrastructural damage.

Hypercontracture in nonbeating myocytes is defined as an additional increase in cell shortening on reoxygenation (52). The myofibrillar contraction (5, 64) is preceded by the uncontrolled calcium influx into the reperfused myocytes (47). With reenergization of the tissue, there is hyperactivation of contractile elements within the cell and hypercontracture (37, 59). In the tissue microenvironment, this leads to membrane disruption and cell death as a result of intracellular force transmission (16). The increased internal stresses within the cytoskeleton of a hypercontracted cell are likely to alter the kinetics of those channels that are modulated by cytoskeletal protein interactions (55). Also, selective degradation of cytoskeletal-associated proteins such as myosin light chain-1 has been shown to occur during reperfusion but not during ischemia (57). These combined effects may render ventricular myocytes highly vulnerable to arrhythmogenic mechanoelectrical coupling during reperfusion.

In conclusion, the results of this study indicate that regionally ischemic hearts are more susceptible to ventricular SIAs during time periods corresponding to phase Ia ischemia, suggesting a possible mechanism for the genesis of the triggered arrhythmias during this period. This study also indicates that mechanoelectrical coupling may contribute to the triggered ventricular arrhythmias during reperfusion after acute ischemia. The latter result suggests that preventative measures against arrhythmogenic mechanoelectric signaling may be beneficial during the administration of thrombolytic therapies.

#### GRANTS

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