Electrophysiological Effects of Myocardial Stretch and Mechanical Determinants of Stretch-Activated Arrhythmias

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Background. Although the existence of myocardial mechano-electrical feedback is well established, the mechanism of arrhythmia induction by ventricular dilatation or stretch remains insufficiently defined. In particular, controversy exists when comparing the arrhythmogenic potential of chronic versus acute myocardial stretch. Also, assessment of cellular electrophysiological effects of myocardial stretch has been incomplete.

Methods and Results. To evaluate the electrophysiological and arrhythmogenic effects of slow versus rapid ventricular wall stretch, we developed an isolated Langendorff-perfused rabbit heart model in which left ventricular (LV) volume can be changed by a computer-controlled servopump. Cellular electrophysiological effects and premature ventricular excitations (PVEs) and their origin produced by the volume increases were assessed by a multiple-site monophasic action potential (MAP) recording system and by volume-conducted ECGs obtained by immersing the entire preparation in a saline-filled tank. Volume was increased either gradually with slow volume ramps (0.1 ml/sec) or suddenly by volume pulses of varying pulse waveforms (three different amplitudes and five different rise velocities) applied randomly 250–350 times to each of eight hearts. Gradual LV volume loading caused gradual decreases in MAP resting and action potential amplitude, whereas rapid, transient volume pulses caused transient depolarizations. Despite similar membrane potential effects of stretch, gradual volume increases rarely (11%) produced PVEs, even with large volume loads, whereas rapid volume pulses of moderate amplitudes regularly triggered PVEs (45–100% of interventions). Logistic regression analysis showed that the probability of PVE occurrence increased independently with both the amplitude and the velocity of the volume increase, with the greatest sensitivity to stretch velocity exhibited at low and intermediate pulse amplitudes. Faster volume pulse rise velocities triggered PVEs at a lower instantaneous pulse amplitude than lower rise velocities, further corroborating the dependence of stretch-activated arrhythmias on the velocity of stretch. In contrast, an increase in the basic ventricular volume had no effect on the probability of PVE occurrence during the volume pulses. The MAP recordings demonstrated spatial variability in the extent of local depolarizations and site of PVE origin; transient depolarizations occurred, and PVEs originated most often in the posterolateral region of the left ventricle.

Conclusions. Membrane depolarization is caused by both gradual and rapid ventricular stretch, but PVEs are more easily elicited by rapid stretch. Regions of greater myocardial compliance that experience greater relative stretch may act as “foci” for stretch-activated arrhythmias during dynamic ventricular loading. These whole-heart data corroborate the existence of stretch-activated membrane channels in ventricular myocardium and may help explain ventricular ectopy under conditions of differential ventricular loading, as in ventricular dyskinesia, or regional muscle traction, as in mitral valve prolapse syndrome. (Circulation 1992;86:968–978)

Ventricular arrhythmias are frequently seen in patients with ventricular dysfunction, such as with dilated cardiomyopathy, ventricular volume or pressure overload, or dysynergic ventricular contraction and relaxation.1–4 One mechanism suggested to cause arrhythmias under these conditions is mechanoelectrical feedback, also known as contraction–excitation feedback.5,6 Mechano-electrical feedback is defined as the development of electrophysiological and possibly arrhythmogenic changes during or after changes in mechanical loading conditions.5–7 Direct evidence from intracellular action potential studies is limited due to technical difficulties in maintaining proper microelectrode impalements during vigorous heart beating or during mechanical manipulations of the preparation. In the few studies available performed in excised mammalian tissue and intact amphibian hearts, mechanical stretch caused shortening of the action potential duration and decreases in diastolic membrane potential.6–12 In some studies, stretch was also shown to cause afterdepolarizations, which in turn were associated with arrhythmias.7,8

Recently, several investigators have investigated the electrophysiological effect of volume increases in intact
mammalian hearts. Lerman et al.\textsuperscript{13} and Calkins et al.\textsuperscript{14} found that monophasic action potential (MAP) durations and refractory periods shortened after an increase in ventricular volume but did not report diastolic potential changes or increased arrhythmias. Both groups made no comments on the electrophysiological effects or arrhythmias that might have occurred during the transition from low to high volume. Hansen et al.\textsuperscript{15} studied the effects of rapid, transient volume increases in an isolated, perfused canine ventricle and noted ectopic excitations during or shortly after the volume pulse. These authors suggested that the volume pulse-related ectopic ventricular excitations may have been triggered by an increased velocity of spontaneous diastolic depolarization; however, they did not record direct electrophysiological indexes to support this interpretation. Dean and Lab\textsuperscript{16} and Franz et al.\textsuperscript{17} recorded left ventricular (LV) ECGs and MAPs in intact pig and dog hearts during transient occlusions of the ascending aorta and noted ectopic ventricular beats within seconds of the aortic clamp.

To reconcile the above cited and, at first sight, apparently conflicting results, we hypothesized that electrophysiological changes capable of triggering ectopic excitations occur only during sudden, transient volume increases; static volume loading may permit the myocardium to adapt to the load increase. To test this hypothesis systematically, we developed a computer servo-controlled, Langendorff-perfused rabbit heart preparation that allowed us to increase LV volume at varying velocities at selected times during the cardiac cycle. To measure regional electrophysiological changes during the mechanical interventions, we designed a new apparatus for continuous and simultaneous recording of MAPs from multiple right ventricular (RV) and LV epicardial and endocardial sites. To further corroborate the origin of mechanically induced ectopic excitations, we immersed the entire preparation into a saline-filled tank equipped with electrodes to record a volume-conducted ECG from the isolated heart.

**Methods**

**Isolated ECG Preparation**

Male New Zealand White rabbits weighing 1.8–2.2 kg were killed by cervical dislocation after intravenous administration of 500 IU of heparin. The chest was opened via a median sternotomy, and the heart was removed with scissors, with a cuff of intact aorta and pulmonary artery still attached. The hearts were immediately arrested by immersion into ice-cold Tyrode’s solution, and the remaining lung, pericardium, connective tissue, and great vessels were removed. After the preparation had been completed, the hearts were weighed in a second beaker containing ice-cold Tyrode’s solution. The hearts had a wet weight of 6.6±0.7 g (range, 5.8–7.5 g). Thereafter, the aorta was cannulated with a flexible polyethylene tube that was flared and ligated by suture to prevent withdrawal of the cannula from the aorta. Perfusion with warm (37°C) modified Tyrode’s solution was started immediately. The composition of the modified Tyrode’s solution was (in mM): 115 NaCl, 4.7 KCl, 2.0 CaCl\(_2\), 0.7 MgCl\(_2\), 28 NaHCO\(_3\), 0.5 NaH\(_2\)PO\(_4\), and 20 glucose. Bovine albumin at a concentration of 0.02 mM was added to the perfusate, which has been shown to delay the process of electrophysiological deterioration.\textsuperscript{18} The perfusate was equilibrated at room temperature with 95% O\(_2–5%\) CO\(_2\), and the pH was adjusted to 7.4. The flow rate was adjusted to maintain a perfusion pressure between 50 and 70 mm Hg, using a variable-speed roller pump (MasterFlex, Cole Parmer Instruments). The average flow rate was 25.8±1.8 ml/min (approximately 4 ml/min/g wet wt) (range, 23–30 ml/min). Time from excision to cannulation of the aorta and initiation of perfusion was approximately 2 minutes. The cannulated and perfused hearts were affixed to a modified vertical Langendorff apparatus (Figure 1). After incision of the left atria, the left ventricles were vented with a short polyethylene tube passed transmurally through the apex with a 20-gauge needle. A deflated latex balloon, mounted on a central stub of the Langendorff apparatus, was fitted through the left atrium and the mitral orifice into the left ventricle. The remaining atrial tissue was wrapped around the stub and secured by a string ligature to keep the preparation in place and the balloon from being herniated. The portion of the central stub inside the balloon had an opening at the bottom (i.d., 4 mm) and small holes drilled into the side of the stub to allow more efficient movement of fluid in and out of the balloon. The balloon was partially inflated with a baseline loading volume of 0.5 ml H\(_2\)O introduced from a syringe through a side-port. A metal ring was positioned under the apex of the heart to provide additional support and serve as common ground for the electrical measurements. A high-fidelity fiberoptic manometer-tipped catheter (Camino Laboratories, San Diego, Calif.) sheathed in a polyethylene tube could be placed into the balloon lumen through the lower of two side-ports. A syringe

![Figure 1. Experimental setup. LV, left ventricle; MAP, mean arterial pressure. (See text for details.)](http://circ.ahajournals.org/)
connected to the upper side-port by polyethylene tubing was used to remove air from the pump system and to introduce static intraventricular balloon volume changes.

To slow the intrinsic heart rate, the atrioventricular (AV) node was destroyed before mounting by radiofrequency energy catherization applied between two electrode points located at the tip of a specially constructed pair of tweezers. This resulted in either a marked decrease in the heart rate or complete AV dissociation with either ventricular asystole or ventricular escape with a rate usually below 50 beats per minute. The hearts were paced by a bipolar platinum electrode hook inserted into the high RV epicardium. Rectangular pacing stimuli of 2-msec duration were generated by the same computer that controlled the experimental protocol (see below). Pacing stimuli were delivered through an isolated, constant-current stimulator (model A360 Stimulus Isolator, WPI, New Haven, Conn.) at twice diastolic threshold strength.

**Servoregulated Volume Pump**

Dynamic intraventricular balloon volume changes were performed by a water-filled piston pump (BD Multiset 5-ml glass syringe) that was encased in plastic housing and positioned above the isolated heart attachments (Figure 1). The piston pump was driven by a DC linear motor (model 517, Applied Engineering, San Jose, Calif.) mounted directly above the piston. Volume displacement of the pump was controlled by an AC-AC linear voltage displacement transducer (model 294-000, Trans-Tek Inc., Ellington, Conn.) that was supported by a linear voltage displacement transducer oscillator-demodulator (model 1000-0012, Trans-Tek Inc.). The variable volume command signal was generated by a computer (Macintosh IIfx) using customized LABVIEW 2 software (National Instruments) that was also used to pace the preparation, monitor the experimental apparatus, and direct experimental interventions. Comparison of the computer-generated volume command signal with the pump linear displacement feedback signal was performed by a custom-designed signal-matching system. The difference between the volume signal and the pump feedback signal resulted in an error signal. This error signal was analyzed to generate a restoring signal that was proportional to the position error plus the integral of the error plus the derivative of the error. The restoring signal was amplified by a high-output power amplifier (model PA-02, Apex Microtechnology Corp., Tucson, Ariz.) that maintained the proper position of the piston pump. The maximum pump response was 9.20 ml/sec with a minimum time to peak corrected volume of 40 msec. The pulse volumes delivered were linear over the experimental range of volume pulses (0.0–1.6±0.1 ml). The distance between the pump piston and the inflow to the balloon was minimized to prevent damping or resonance of the system. Volume pulse shape, duration, and timing during the cardiac cycle, relative to the last pacing stimulus, were all controlled by the computer. A comparison between the command signal and the recorded feedback signal verified that the desired volume pulse waveforms were delivered to the preparation with high fidelity without damping or oscillations (Figure 2).

**MAP Recording**

A plastic ring with six evenly spaced radial extensions was mounted around the pump casing. Three of these extensions held cantilever arms that were constructed from stainless-steel surgical tubing (i.d., 1.5 mm) and attached to a coiled-wire spring mechanism in the distal end of the radial extensions (Figure 1). Custom-made Ag-AgCl bipolar contact MAP electrodes (EP Technologies, Mountain View, Calif.) were mounted in the distal end of the cantilever arms. Constant contact pressure between the MAP electrode cantilever arms and the heart surface was maintained by adjusting the tension of the springs in the cantilever arms. Electrical continuity between the MAP reference electrode and the heart was provided with a foam rubber sponge that was fitted around the distal electrode assembly and soaked in Tyrode’s solution. One electrode was placed on the right ventricle and one each on the LV midanterior and lateral free walls, respectively. MAP recordings obtained with these contact electrodes have been shown to reproduce the time course of transmembrane action potentials and of relative changes in transmembrane resting and action potential amplitudes with high accuracy. An endocardial MAP electrode was placed into the left ventricle before the heart was mounted on the pump-electrode stand. A thin, insulated copper wire (o.d., 0.5 mm) was guided into the left ventricle through the atrium and inserted through the midanterior portion of the ventricular free wall. The wire was pulled through the wall until an Ag-AgCl pellet (o.d., 1.5 mm) attached to the distal end of the wire was firmly pressed
against the LV endocardium (Figure 1, inset), which was then held under constant pressure by attaching the endocardial electrode wire to one of the remaining free spring-coiled cantilever arms. The MAP electrode pellet was insulated except for the area that rested against the endocardial surface. The reference lead from the nearest epicardial MAP electrode bipole was used as the reference for the endocardial electrode.

After the heart was mounted and had stabilized for 15 minutes, the cantilever arms were positioned so that the epicardial MAP electrodes rested on the surface of the heart. Care was taken to place the epicardial electrodes in a position perpendicular to the ventricular surface. The spring tension of each MAP cantilever arm was adjusted using the minimum tension, which resulted in a stable MAP signal. Similarly, the tension in the endocardial electrode cantilever arm was adjusted until a stable signal developed. In all experiments, the amplitude and configuration of the MAP recordings remained essentially unchanged for periods of 3 hours and longer. All MAP recordings were preamplified by a multichannel, differential, DC coupled amplifier with automatic offset control and internal 5-mV calibration (model 1009, EP Technologies).

Recording of Volume-Conducted ECG

Simultaneous with the epicardial and endocardial MAP recordings, a volume-conducted ECG was recorded by complete immersion of the heart into a bath of warmed Tyrode’s solution that was thermally equilibrated with the myocardial perfusion fluid (37±1°C) using digital temperature probes mounted in the external bath and the inflow port to the coronary arteries. Three 2-mm Ag-AgCl pellets were positioned in triangular arrangement—one on the bottom and two on the side walls of the ECG chamber, which is similar in size to the width of a rabbit’s thorax (i.d., 12 cm). The signal from this simulated “Einthoven” configuration (usually lead II) was amplified by a standard ECG amplifier and showed a configuration similar to that recorded from an intact rabbit’s chest. Immersion of the preparation in the bath did not influence the quality or amplitude of the MAP recordings.

Experimental Protocols

LV pressure, epicardial and endocardial MAP signals, and the volume-conducted ECG were recorded continuously while the left ventricle was subjected to either gradual or abrupt volume loading, according to three different protocols. In protocol A (five experiments), hearts were paced electrically from the RV base while the LV volume was increased gradually via the intraventricular balloon as a ramp of linear volume increase, which reached peak volume over at least 10 paced beats, was maintained at peak volume for at least 20 beats, and was returned to baseline at the same rate at which it had been increased. In protocol B (two experiments), short rectangular volume pulses of 50-msec duration were administered during electrical diastole to determine threshold phenomena of mechanical stretch. This included determination of the strength–interval relation of stretch-activated PVEs by administering rectangular volume pulses at successively decreasing coupling intervals while adjusting the pulse amplitudes to maintain threshold levels until absolute refractoriness to the mechanical stimuli was encountered.

Protocol C was designed to analyze in greater detail the effects of amplitude versus velocity of volume increases. Trapezoidal volume pulses of three different amplitudes (0.25, 0.5, and 0.75 ml), each with four different rise velocities (1, 2, 5, and 10 ml/sec), were administered to the left ventricle at two different basic volumes of 0.5 and 1.0 ml (Figure 2). The volume pulse amplitudes and velocities were chosen based on pilot studies, which suggested that the chosen parameters would include combinations that would nearly always trigger PVEs, as well as combinations that rarely would. The 12 possible combinations were delivered in randomized fashion at either low or high basic volumes for 195±28 pulses per heart, totaling 1,427 volume pulses administered in eight experiments. The maximum volume pulse hold-time (∂) was kept constant at 70 msec and the volume pulse rise-time (∂) varied from 120 to 160 msec (149.8±19.5 msec), depending on the delay time, the rise velocity, and the available cycle length. The paced cycle length was adjusted to be shorter than the ventricular escape cycle length and ranged from 700 to 1,000 msec (830.4±96.5 msec). Volume pulses were delivered after each eighth electrically paced beat with a delay (d) that depended on the rise time of the volume pulse and the available cycle length.

Statistical Analysis

The probability with which the different volume pulse configurations contributed to the occurrence of a PVE was assessed by logistic regression analysis. This analysis considered individually and by multivariate analysis the effect of each volume pulse waveform variable: V (the initial volume), (the delay from the last electrical stimulus to volume pulse onset), (the volume pulse amplitude), ROR (the rate of rise of the volume pulse calculated as the volume rise time [∂] divided by ), and f (the volume pulse fall time). A value of p=0.05 was used to reject the null hypothesis. Numeric analysis and graphic output of the logistic regression analysis were produced with JMP software from SAS Institute, Cary, N.C.

Results

Typical baseline recordings from the isolated rabbit heart, with simultaneous MAP signals at four different sites (two LV epicardial, one LV endocardial, and one RV epicardial site), LV pressure, and volume conductor ECG are shown in Figure 3. MAP recordings had sharp upstrokes, smooth action potential waveforms, and flat diastolic potentials, with no evidence for waveform irregularities that might have been caused by the motion of the beating ventricles. The preparation was paced from the basal RV epicardium (in this example, at a cycle length of 600 msec), and the activation sequence of the four MAP recordings is consistent with high RV pacing, as is the simultaneously recorded volume-conductor ECG that mimics lead II and shows an inferior QRS axis. PVEs occurred rarely during baseline conditions; the background PVE occurrence rate in all experiments was 4.7% of the total number of paced beats.
Electrophysiological Effects of Gradual Volume Increases

Gradual increases in LV volume resulted in simultaneous gradual decreases in diastolic and systolic amplitude of MAPs recorded from the left ventricle but not in MAP recordings from the unloaded right ventricle (Figure 4). When the LV volume was returned to baseline, the LV MAP signals also fully reversed to their baseline values. PVEs occurred during 21% of the gradual LV volume increases but only rarely (6.7%) during the period of sustained volume increases.

Electrophysiological and Arrhythmogenic Effects of Sudden Volume Increases

Figure 5 shows a series of rectangular volume pulses of successively increasing amplitude, which were applied to the left ventricle in the absence of electrical stimulation. The preparation had complete AV block and, before the volume pulse interventions, showed only infrequent ventricular escape beats. The volume pulses induced transient diastolic membrane depolarizations that increased progressively in magnitude, parallel to the increase in volume pulse amplitude. Above a certain amplitude, each transient depolarization was associated with a PVE, i.e., the preparation was “paced” by the volume pulses.

Pulse–Interval Relation

During regular electrical pacing, the sensitivity of the myocardium for stretch may vary with the duration of the diastolic interval. The probability of PVE occurrence was therefore examined as a function of the delay between the last electrical stimulus and the onset of the volume pulse. Figure 6 demonstrates that within the diastolic interval duration of 250–1,000 msec (which always exceeded the action potential duration), the pulse–interval relation for PVE triggering was flat. However, only when the volume pulses encroached onto the repolarization phase of the preceding action potential was a sharp rise in the volume pulse threshold for triggering PVEs observed.

Mechanical Determinants of PVE Occurrence

The previous observations suggest that rapid volume pulses are more effective in triggering PVEs than are slow, gradual volume ramps. We therefore applied LV volume pulses of different rise velocities and amplitudes. Figure 7 compares the arrhythmogenic effect of two volume pulses of identical amplitude (0.5 ml) but different rise velocities (2 and 10 ml/sec). The volume pulse with a relatively slow rate of rise caused transient depolarizations in the LV MAP recordings (arrows) but no PVE (Figure 7A). A volume pulse of identical amplitude but faster rate of rise also caused transient...
depolarizations (arrows), but in contrast to the former example, the more rapid depolarization was associated with a PVE (Figure 7B). To evaluate the dependence of stretch-activated PVE occurrence on both amplitude and velocity of the stretch in a systematic fashion, an average of 265 volume pulses of varying rise velocities and amplitudes were delivered to each left ventricle randomly (1,427 pulses in all) and the data were submitted to logistic regression analysis. Figure 8 shows the probability of PVE occurrence as a bivariate function of volume pulse amplitude (0.25, 0.5, and 0.75 ml) and volume pulse rise velocity (1, 2, 5, and 10 ml/sec) for all eight experiments. The pulse amplitude was the strongest predictor of PVE occurrence, with probabilities reaching near-saturation \( p=0.97-0.99 \) at the greatest pulse amplitudes of 0.75 ml. The velocity of volume increase also contributed significantly to the probability of PVE occurrence, with the greatest effect of pulse velocity at low and intermediate pulse amplitudes \( p<0.0001 \). In contrast, the basic (initial) volume \( V_i \) had no effect on the probability of PVE occurrence over the entire range of volume pulse parameters tested \( p=0.89 \) for \( V_i \) of 0.5 versus 1.0 ml. There was a small but significant positive effect of the volume pulse delay on PVE occurrence. The volume pulse fall time had no effect on the probability of PVE occurrence during or after the volume pulses. There was no significant interaction effect between pulse volume amplitude and rise velocity \( (PV*ROR) \). Table 1 lists the relative effects and significance levels of each variable as analyzed by multiple logistic regression.

**Dependence of the PVE Trigger Volume on the Rate of Volume Increase**

The above protocol compared the arrhythmogenic capacity of three discrete, predetermined volume am-
plitudes combined with four discrete, predetermined rates of volume rise. This analysis does not yield information whether, for a given pulse waveform, the maximum pulse amplitude was necessary to trigger the PVE or whether the PVE may have occurred before the peak amplitude was reached, i.e., at a somewhat lower pulse volume. To examine the effect of rate of volume rise on PVE trigger volume in a more analogous fashion, the data were also analyzed as schematically depicted in Figure 9. PVE trigger volumes (the actual volume at which the PVE was initiated during the rising phase of

![Figure 6](image-url) **FIGURE 6.** Plot of volume pulse threshold for producing premature ventricular excitations (PVEs) as a function of pulse delay time. Rectangular volume pulses of 50-msec duration were delivered at successively shorter intervals after the preceding action potential. Pulse amplitude was adjusted in 0.02-ml increments until a PVE was elicited in at least two of every three attempts.

![Figure 7](image-url) **FIGURE 7.** Tracings of dependence of premature ventricular excitation (PVE) trigger volume on the rate of volume increase. Left panel: A left ventricular (LV) volume pulse of 0.5 ml with a relatively slow rate of rise (2 ml/sec) caused transient depolarizations in the LV mean arterial pressure recordings (arrow) but no PVE. Right panel: A volume pulse of identical amplitude but faster rate of rise (10 ml/sec) also caused transient depolarizations (arrow), but, in contrast to the former example, this more rapid depolarization was associated with a PVE.

![Figure 8](image-url) **FIGURE 8.** Three-dimensional representation of the predictive powers of volume pulse amplitude and rise velocity for inducing a premature ventricular excitation. The data were derived from multiple logistic regression analysis. The vertical ordinate is the probability range from 0 to 1, with 1 equaling 100% probability.
Table 1. Effect Test of Stretch Pulses

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PV*ROR, interaction effect between pulse volume amplitude and rise velocity.

Relative significance of the effects of stretch pulse variables on stretch-induced premature ventricular excitations as determined by multiple logistic regression analysis. (See text and Figure 2 for further details and explanation of variables.)

The volume pulse) were calculated as the product of the rate of rise and the coupling interval of PVE occurrence. As hypothesized, a faster rate of volume rise caused the PVE to occur earlier during the volume rise, i.e., at a smaller actual pulse volume. This is quantitatively shown in Figure 9, which presents the results averaged from all eight experiments.

Origin of Stretch-Induced PVEs

The origin of the volume pulse-induced PVEs was determined by two independent methods: first, by the activation sequence of the PVE as derived from the three LV and one RV MAP recordings and, second, by the morphology of the simultaneously recorded volume-conducted ECG (Figure 9). Judged by these methods, of a total of 1,020 PVEs induced by rapid LV volume increases, 773 PVEs (75.8%) originated from the left ventricle, 64 (6.3%) originated from the right ventricle, and 183 (17.9%) had an undetermined origin. To exclude the possibility that the PVEs during volume pulses were caused by mechanical interaction between the MAP electrodes and the epicardium, all MAP electrodes were lifted off the preparation, and the same protocol was repeated (three experiments). Volume pulses continued to induce PVEs of the same ECG morphology as was noted while the MAP electrodes were in place (Figure 10).

Discussion

This study demonstrates that sudden volume expansion of the left ventricle elicits LV PVEs that are tightly coupled to the volume pulse. Although previous studies have described PVEs in response to sudden volume pulses,15,16 evidence for the electrophysiological mechanism of these PVEs was mainly indirect. By examining the arrhythmic response to a variety of different pulse waveforms and by recording MAPs from epicardial and endocardial sites, we were able to describe in more detail the determinants of stretch-induced PVEs as well as a likely electrophysiological mechanism for their genesis.

Determinants of Stretch-Induced PVEs

PVE occurrence was determined by both the amplitude and the velocity of the volume increase. If ventricular volume was increased gradually over several beats, PVEs occurred rarely despite an almost twofold increase from baseline volume. In contrast, rapid, near-rectangular volume pulses consistently produced PVEs and, above a distinct threshold volume, were able to "pace" an otherwise asymptotic ventricle. Logistic regression analyses of the effect of different volume pulse waveforms showed that the probability of PVE occurrence increased independently with the amplitude and the rise velocity of the volume pulse. In keeping with the dependency of PVE induction on the pulse velocity was the observation that during faster volume pulses, the PVE occurred earlier during the volume pulse, i.e., a greater rise velocity decreased the volume increment required to trigger the PVE. In contrast, a twofold increase in the baseline volume had no influence on the probability of PVE occurrence during the volume pulses. This underscores the fact that static volume increases are not arrhythmogenic per se, nor do they increase the arrhythmogenic response to pulsatile stretch.

These observations unify previous, apparently conflicting observations on the electrophysiological effects of mechanical loading. Although some investigators have demonstrated an association between volume expansions and ectopic beats,15,17 others have found no such correlation.15,14 Those who failed to observe PVE induction by volume loading had examined only the electrophysiological effect of gradual or static volume increases15,14 and did not measure or report the electrophysiological changes or arrhythmias that might have occurred during the transition from low to high volume. In contrast, investigators who studied the effects of

Figure 9. Left panel: Schematic illustrating the effect of rate of volume increase on actual premature ventricular excitation (PVE) trigger volume. Volumes were calculated as the product of the rate of rise and the time of the PVE occurrence. According to our hypothesis, the slower rate of volume rise (dashed line) should result in a greater trigger volume (V2) than the faster rate of volume rise (solid line, V1).

Right panel: Data from all eight experiments demonstrating decrease in trigger volume with increase in pulse velocity.
rapid, transient volume increases\textsuperscript{7,15,17} all noted PVEs during or shortly after the volume pulse.

**Diastolic and Systolic MAP Changes in Relation to the Duration and Timing of Stretch**

Stretch caused a decrease in diastolic potential, regardless of whether stretch was applied transiently by short volume pulses or for a longer period by gradual and sustained volume loading. During short volume pulses, the depolarizations were transient, reflecting the short duration of the stretch. During gradual sustained volume increases, the decrease in diastolic potential occurred slowly and was maintained throughout the loading phase. Volume pulses that resulted in a PVE caused stretch-induced voltage changes that appeared as prepotentials (Figure 4) while volume pulses administered at the end of the action potential caused afterdepolarizations. Thus, whether stretch produces prepotentials, afterdepolarizations, or diastolic depolarizations depends on the timing of the stretch pulse with respect to the cardiac cycle. Similar observations were made by Lab\textsuperscript{8} in isolated amphibian hearts. The stretch-induced afterdepolarizations are not necessarily identical with, nor reflect the same mechanism, as the "classic" afterdepolarizations that occur only in the aftermath of a preceding, triggering action potential.\textsuperscript{23} Stretch also influenced the action potential amplitude. Sustained volume loading decreased the MAP amplitude for as long as stretch was applied. These observations in the mammalian heart are consistent with those made previously in isolated frog myocardium\textsuperscript{9} and in situ canine hearts.\textsuperscript{17}

Stretch-induced depolarizations have been attributed to conductance increases in either nonselective or selective ion channels.\textsuperscript{24,25} Hansen et al\textsuperscript{26} demonstrated in isolated canine ventricles that stretch-activated arrhythmias could be suppressed by gadolinium chloride, a potent nonselective calcium channel blocker, but not by nifedipine or verapamil, which block $I_{Ca}$ channels. Craelius et al\textsuperscript{25} identified a stretch-activated channel in isolated cardiac myocytes that is characterized by a nonselective increase in cation conductance and a reversal potential of $-32$ mV. This stretch-activated channel maintained its open state for long periods of stretch without any signs of adaptation or "fatigue." This may explain our observation that decreases in membrane resting potential were observed during both sudden and sustained stretch and that these depolarizations reversed only with reversal of the volume load.

**Link Between Stretch-Induced Diastolic Depolarizations and Arrhythmias**

Although both gradual and rapid volume loading of the ventricle produced decreases in the MAP diastolic potential, only the latter triggered PVEs. The dependency of PVE induction on the velocity of stretch was strongest in the midrange of pulse amplitudes tested; a minimum (threshold) magnitude of stretch was required even for rectangular pulse waveforms, and large pulse amplitudes nearly always triggered PVEs within the range of pulse velocities tested. It was not possible to define the slowest volume increment that triggered PVEs because the escape interval of the preparation precluded insertion of very long pulses within the available diastolic interval. However, the facts that slow volume ramps administered over many beats caused PVEs only very infrequently despite twofold to threefold increases in LV volume and that twofold increases in basic volume did not increase the probability of PVE occurrence during pulsed stretch strongly suggest that a minimum stretch velocity is required for arrhythmia induction.

Hansen et al\textsuperscript{15} suggested that stretch-activated PVEs may be triggered by an increased rate of phase 4 depolarization. Their interpretation was based on the observation that PVEs did not always coincide with the stretch pulse but rather demonstrated a greater probability of occurrence within a statistical window during

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure10}
\caption{Tracings of simultaneous mean arterial pressure (MAP) (three left ventricular [LV] epicardial sites) and ECG recordings during electrical stimulation and LV volume pulse before and after lifting off the MAP electrodes. The LV volume pulse produces premature ventricular excitations of identical ECG morphology regardless of whether the MAP electrodes rested on the heart's surface.}
\end{figure}
which no PVEs occurred spontaneously. In our experimental model, PVEs always occurred in close temporal association with the rising phase of the volume pulse. Probably because our catecholamine-free perfusate background arrhythmic activity or ventricular escape beats were nearly absent (<5.6%) within the paced cycle lengths made it easy to ascertain a direct relation between volume pulses and PVEs. However, an increased delay between the last electrically paced beat and the onset of the volume pulse had a small but significant positive effect on the probability of PVE occurrence. Therefore, we cannot exclude the possibility that spontaneous phase 4 depolarization contributed in some part to these stretch-activated PVEs, but this delay-dependent increase in susceptibility for stretch may also be due to other, not yet defined mechanisms. We never observed accelerated phase 4 depolarization after subthreshold stretch pulses; diastolic depolarizations occurred only after the onset of stretch and always were confined to the period of stretch. The velocity of release from stretch, previously shown to alter membrane potential, also cannot account for PVE induction because our logistic regression analysis showed no effect of variations in volume pulse fall time on PVE occurrence. On the other hand, a greater volume pulse rise velocity shifted the PVE trigger volume toward the left of the rising phase of the volume pulse, i.e., to a lower instantaneous “take-off” volume. This not only supports the dependency of the PVE induction on the velocity of stretch but further corroborates a direct association between stretch and PVE induction. Based on the sum of these observations, we favor the hypothesis that the PVEs occurred in direct response to stretch-induced membrane depolarizations.

The myocardial response characteristics to transient volume pulses were surprisingly similar to those known for electrical stimuli. Asystolic preparations could be ventriculatly paced by rapid ventricular volume pulses, demonstrating a threshold phenomenon similar to electrical stimuli. The volume pulse threshold for triggering PVEs was flat during the entire period of electrical diastole but rose sharply toward shorter coupling intervals that encroached on the preceding repolarization phase; this interval relation for mechanical stimuli closely resembles the strength–interval relation of electrical stimuli. Electrically induced depolarizations also must occur with both a sufficient amplitude and a sufficient velocity to reach the threshold for propagated excitation; gradual depolarizations may fail to reach the threshold for self-regenerating depolarization and cause merely a local electrical response. This stimulus-response behavior is ubiquitous in excitatory tissues, including nerve fibers, and has been explained on the basis of the Hodgkin and Huxley kinetics; slow depolarizations allow membrane channel inactivation processes to preempt membrane channel activation processes.

Site of PVE Origin

Due to the limited number of MAP electrodes placed on the ventricles, the exact site of origin of stretch-induced PVEs could not be determined. All that could be established by the sequence of MAP activation times and ECG morphology was that the vast majority of PVEs originated in the left ventricle. Considering the fact that the left ventricle was submitted to global volume loading, one may wonder if there can be any consistent site of stretch-activated PVEs. The rather uniform MAP activation sequence and ECG morphology observed during repeated volume pulse administrations suggest that this was indeed the case. A possible explanation is that even during global volume loading, certain ventricular wall segments experience more stretch than others because of differences in ventricular wall thickness, compliance, and geometry.

Validity of Electrophysiological Changes Recorded by the MAP Contact Electrode Technique

The electrophysiological effects of sudden or slow ventricular volume increases were measured by the MAP contact electrode technique rather than by intracellular microelectrode recordings. We have previously demonstrated in isolated rabbit septum preparations that such MAP recordings, although of smaller amplitude than intracellular measurements, accurately indicate the time course of membrane repolarization and relative changes in membrane resting and action potential amplitude. However, in this whole-heart study, the possibility must be addressed that transient depolarizations in the MAP recordings during transient volume pulses may represent movement artifacts.

The microelectrode technique is itself highly susceptible to movement artifacts and therefore cannot be used to validate the MAP recordings in the vigorously beating, intact heart. Based on the following observations, however, we believe that the sustained and transient depolarizations recorded by the MAP electrodes reflect true cellular electrophysiological events and not artifacts. First, movement artifacts would most likely be those that are caused by movement-induced instability of the electrode–tissue contact. Changes in contact pressure between the MAP electrode and the myocardium must occur even during the normal cardiac contraction–excitation cycle. However, transient depolarizations or other MAP irregularities were never observed in baseline recordings. Second, LV volume pulses produced voltage changes of equal polarity in both the endocardial and epicardial LV MAP recordings, although changes in electrode contact pressure would be expected to occur in opposite directions at the inner and outer surfaces of the expanding ventricle. Third, RV MAP recordings showed neither transient or sustained depolarizations during LV volume expansions, although the deflated RV wall rested on the intraventricular septum and thereby followed the excursions of the left ventricle. Fourth, there was an extremely tight correlation between the timing of stretch-induced transient depolarizations and the occurrence of propagated PVEs. The majority of PVEs (>75%) originated from the stretched LV myocardium during or at the peak of the volume pulses, with <10% originating from the right ventricle. Fifth, volume pulses produced PVEs of identical ECG morphology (indicating LV origin) even when the MAP electrodes were lifted off from the preparation. This excludes the possibility that the PVEs were caused by friction between the contact electrode and the expanding ventricular wall segment.

Clinical Relevance of Mechanoelectrical Feedback

There are several clinical observations that implicate that changes in hemodynamic loading or sudden me-
mechanical disturbance of the ventricle produce electrophysiological effects. Waxman et al. reported that Valsalva maneuvers can both initiate and terminate ventricular tachycardia. Common clinical experiences such as resuscitation by precordial thumb or by direct cardiac massage likewise suggests a link between mechanical perturbations of the myocardium and electrophysiological effects. Even the occurrence of PVEs often observed during intracardiac catheter manipulation is testimony for the mechanical susceptibility of myocardial tissue.

Although volume changes of the magnitude applied in this experimental preparation are unlikely to occur in the in situ heart, myocardial stretch comparable in magnitude to that administered in our experiments to the entire ventricle may occur in vivo on a regional basis. Ischemic wall segments or wall segments stunned by a previous ischemic episode are less contractile than normal myocardium, yet they are exposed to the same cyclic increases in intraventricular pressure as the normal wall segments. This can cause bulging of the ischemic segment during systole and during the isovolumic relaxation phase when blood is “ejected” into the segment of lesser resistance. The regional stretch occurring under those conditions could be comparable to the one produced globally in our experiments. Mitral valve prolapse may cause rhythmic papillary muscle traction at the end of systole, and the resulting focal stretch may be responsible for PVEs commonly seen in this syndrome. Ventricular dysynchrony may also be due to deviations from the normal pattern of ventricular depolarization that dictates the sequence of ventricular contraction and relaxation. Wall segments that are activated earlier than the bulk of ventricular muscle will also relax earlier. These segments will have relatively less elastance with which to carry the burden of peak systolic intraventricular pressure and may therefore undergo regional stretch. Each of the above-listed conditions would be aggravated by adrenergic stimulation that increases intraventricular pressure and increases contractility in normal myocardium more than that in diseased segments. Thus, mechanoelectrical feedback may be operative in a variety of clinical conditions and may play a significant role in the genesis of arrhythmias.

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