Stretch-Induced Arrhythmias in the Isolated Canine Ventricle
Evidence for the Importance of Mechanoelectrical Feedback

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Alterations in loading conditions and muscle length influence the electrophysiology of ventricular myocardium and may play a role in arrhythmogenesis in globally dilated or dyskinetic ventricles. To test the hypothesis that stretch can initiate arrhythmias in normal myocardium, the response to graded mechanical stretch was studied in seven isolated blood-perfused canine ventricles. After eight conditioning contractions produced by His bundle pacing (2 Hz), global stretch of the ventricle was produced by a servocontrolled pump that abruptly increased ventricular volume by a precise amount (ΔV) during early diastole and then returned ventricular volume to the initial holding volume (V_i). Ventricular premature contractions were readily produced; ventricular couplets and short runs of ventricular tachycardia were occasionally elicited. The probability of a stretch-induced arrhythmia was determined from multiple alternating sequences in which a stretch of known amplitude (ΔV) or no stretch was delivered. As ΔV was increased, the probability of a stretch-induced arrhythmia was low initially, increased sharply after a threshold was exceeded, and approaching 100% with physiological volumes. With V_i set to a standard value of 20 ml, corresponding to end-diastolic pressure of 5.3±5.2 mm Hg (mean±SD), the ΔV resulting in a 50% chance of a stretch-induced arrhythmia (ΔV_50) was 15.0±1.6 ml. A decline in ΔV_50 was consistently observed when V_i was increased. While ΔV_50 values were remarkably similar (10.7% coefficient of variation), the pressure at the time the ventricular premature depolarization was triggered was highly variable for different ventricles; this finding suggests that myocardial strain is more important than absolute level of wall stress in the initiation of these arrhythmias. These results demonstrate that myocardial stretch predictably initiates arrhythmias and that the susceptibility to stretch-induced arrhythmias is enhanced by ventricular dilatation. Thus, ventricular ectopy in patients with regionally or globally dilated hearts may arise, in part, by a mechanism of myocardial stretch. (Circulation 1990;81:1094–1105)

It is commonly accepted that serious ventricular arrhythmias are caused by abnormalities in impulse formation and conduction; however, these important electrophysiological mechanisms fail to explain why lethal arrhythmias most commonly arise in patients with severe heart failure and dilated ventricles. A number of factors predispose such patients to arrhythmias. Structural abnormalities, especially inhomogeneities of the myocardium, favor the development of reentrant arrhythmias. Metabolic derangements, such as hypokalemia or hypomagnesemia, are especially prevalent in patients treated with diuretics and have been implicated as a cause of ventricular arrhythmias associated with congestive heart failure. Other pharmacologic agents used in the treatment of heart failure, including digitalis, β-adrenoceptor agonists, and phosphodiesterase inhibitors, are known to promote serious ventricular ectopy. Increased sympathetic activity, a normal compensatory response to depressed cardiac output, is strongly associated with ventricular arrhythmias; indeed, high levels of plasma norepinephrine have been correlated with poor outcome in patients with congestive heart failure. Mechanical dilatation, which is a common feature of patients most

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at risk for serious ventricular arrhythmias and sudden death,\textsuperscript{3–7} has an unproven but potentially important role in the pathophysiology of these arrhythmias. The notion that mechanical dilatation can influence the electrical behavior of the heart ("mechanoelectrical feedback") is well established.\textsuperscript{19} Myocardial stretch during the action potential has been observed to modulate the action potential duration,\textsuperscript{20–23} whereas transient stretch during diastole has been shown to result in depolarization,\textsuperscript{24,25} which can be sufficiently large to trigger action potentials.\textsuperscript{23,26,27} In the intact heart, diastolic stretch might therefore elicit ventricular arrhythmias. Frequent occurrence of such stretch-induced arrhythmias (SIAs) may by itself result in serious morbidity (e.g., symptoms of increased heart failure or angina), especially in patients with diminished cardiac function. More importantly, arrhythmias induced by diastolic stretch could in turn trigger more serious cardiac arrhythmias such as ventricular tachycardia or fibrillation.

Indeed, afterdepolarizations and ventricular arrhythmias have been observed in association with regional wall motion abnormalities with acute occlusion of the aorta\textsuperscript{23,27} or pulmonary artery\textsuperscript{26} in animal models. Changes in monophasic action potential duration during valvuloplasty procedures provide additional evidence of mechanoelectrical feedback in intact human hearts.\textsuperscript{28} However, the experimental interventions used in these studies primarily produce a pressure overload and, therefore, may have limited implications regarding arrhythmogenesis in dilated volume-overloaded hearts. Volume loading of isolated normal ventricles has been associated with, at most, minimal or even no apparent mechanoelectrical feedback effect.\textsuperscript{29–32} Therefore, the importance of mechanoelectrical feedback in the genesis of serious ventricular arrhythmias remains unproven.

We addressed the following questions in isolated canine ventricles subjected to graded mechanical stretch produced by a volume servopump: 1) Does transient stretch applied during diastole result in ventricular arrhythmias? 2) What diastolic changes in volume or pressure are required to elicit ventricular premature depolarizations? 3) Do SIAs correlate better with changes in volume or with changes in pressure? 4) Are the requirements for SIAs similar early and late in diastole? 5) Does volume loading alter the sensitivity of the heart to SIAs? In addition to evaluating the determinants of SIAs by addressing these questions, we also suggest a unified mechanism whereby such arrhythmias might be elicited.

**Methods**

**Animal Preparation**

A total of seven experiments were performed with the isolated canine heart preparation schematically illustrated in Figure 1. The methods used to isolate and support a canine heart were modified after those described by Suga and colleagues.\textsuperscript{33,34} Two adult mongrel dogs were anesthetized with a combination of morphine SO\textsubscript{4} (2 mg/kg i.m.) and \textalpha-chloralose (100 mg/kg i.v.). This method of anesthesia has minimal effect on pump function\textsuperscript{35} and the electrophysiology of the left ventricle.\textsuperscript{36} The chest of the donor dog (27.0±4.1 kg) was opened by median thoracotomy under artificial ventilation, and the pericardium was incised and cradled. Both dogs were then anticoagulated with intravenous heparin (200 units/kg); the support dog also received indomethacin (2 mg/kg) and diphenhydramine (2 mg/kg) prophylactically for prevention of hypotension and low pressure pulmonary edema. The subclavian artery and right atrium of the donor were then cannulated and connected to the femoral artery and vein, respectively, of the support dog for cross circulation. A catheter was inserted into the brachiocephalic artery of the donor dog and connected to a pressure transducer (model P-23ID, Gould, Cleveland, Ohio) to monitor coronary perfusion pressure,
which was held constant at 80 mm Hg by a servocontrolled peristaltic pump (model 1215, Harvard Apparatus, South Natick, Massachusetts). A heat exchanger was used to warm the blood to 37°C. After cardiopulmonary bypass was initiated, the remaining vascular connections were ligated, and the donor heart was rapidly excised and promptly mounted. The left ventricle was vented, and the mitral apparatus was excised. A compliant fluid-filled balloon attached to a metal adapter was then fitted to the left ventricular chamber and secured to the mitral annulus. A micromanometer-tip catheter (model SPC-330A, Millar, Houston, Texas) positioned within the balloon measured the instantaneous left ventricular pressure. The other end of the balloon adapter was connected by a metal conduit to a servoregulated volume pump system. Negative pressure (−10 mm Hg) was applied to the vent to drain Thesbian flow of the left ventricle to ensure a satisfactory fit between the intracavitary balloon and chamber. Absolute left ventricular volume can be measured accurately, to within 0.2 ml, by this method.37 A vent was also placed in the right ventricular apex to drain venous blood, which was collected by a funnel connected to the venous return line. The atrioventricular node was surgically ablated38 through a right atrial incision, and pacing electrodes were attached to the right ventricular endocardium in the region of the bundle of His. A pair of electrodes was also sutured to the epicardial surface, one near the base and another near the apex of the anterior wall, to provide a ventricular electrogram.

Servoregulated Volume Pump

The ventricular servoregulated volume pump consisted of a hydraulic piston (2.5-in. bore, 2-in. stroke) driven by a linear motor (model 420, Ling Electronics, Anaheim, California). A resistive linear displacement transducer (model SLF-S-50-1, Waters, Wayland, Massachusetts) sensed the position of the piston; its output was calibrated to measure absolute balloon volume (linearity ± 0.1%). A specially designed electronic circuit continuously compared the voltage output of the volume sensor with that of a volume command signal; the resulting volume error signal was amplified (model TPA-1000, Ling Electronics) and provided the electrical current to the linear motor as required to clamp the piston to the desired volume. The volume command signal was provided by a hybrid high-speed digital computer (80386 Intel, Santa Clara, California), which calculated the desired volume and converted it to an analog voltage signal, by use of a 12-bit analog-to-digital converter, every 2 msec. This system could track a 10-ml sine wave of 15 Hz with less than 1% error of amplitude and no measurable phase lag.

Experimental Protocol

To define the mechanical properties of the ventricles, measurements of left ventricular pressure and volume were initially acquired with the ventricle beating isovolumetrically at a pacing frequency of 2 Hz. The left ventricular volume was adjusted as required to achieve end-diastolic pressures ranging between 0 and 25 mm Hg. From such data, end-systolic and end-diastolic pressure-volume relations were defined as described below.

Programmed electromechanical stimulation was performed according to the pattern diagrammed in Figure 2. The timing of all electrical stimuli and volume changes were generated by the computer. Each sequence was initiated by electrically stimulating the left ventricle from the His electrodes at a standard frequency of 2 Hz. Electrical stimulation was performed at twice the diastolic threshold by using an electrically isolated 2-msec square wave of constant current. During this “priming” period, left ventricular volume was held constant at a specified initial holding value (V0) as a minimum of eight priming electrical impulses were delivered. At a specified time (Δt) after the final electrical stimulus, the left ventricle was subjected to either a quick stretch (stretch) or no stretch (control) as described below. The computer was programmed to alternate automatically between control and stretch sequences. The stretch consisted of a ramp increase in left ventricular volume of specified amount (ΔV). This volume increase occurred at constant rate over a fixed time interval of 100 msec; thus, actual rates of volume change varied depending on the value of ΔV. The volume was generally held at the maximum (Vf + ΔV) for 50 msec, although the stretch duration was specifically varied in certain protocols. After the ventricle was held at the peak stretch volume for the specified time, volume was returned at constant rate to V0 over the next 100 msec. The response to the stretch was monitored during a 2,000-msec period beginning with the onset of the volume increase (Figure 2). During this response period, the ventricle was not electrically stimulated. The control sequence that preceded each stretch sequence was similar.
except ΔV was set to 0 ml. When the response period was completed, a new sequence was immediately initiated.

Under standard conditions, \( V_i \) was 20 ml and \( \Delta t \) was set to 300 msec. We chose this interval because ventricular escape beats were unlikely to occur this early after cessation of pacing. In selected ventricles in which ventricular escape consistently occurred late, additional data were collected by delivering a volume change 600 msec after the final priming stimulus. We specifically chose to study all ventricles at a relatively low \( V_i \) (20 ml) to avoid overdistension during stretches and to minimize stretch effects during the priming period. The amplitude of ΔV was varied in random order (range, 0–22 ml). Thus, under standard conditions, the volume at peak stretch \((V_i+\Delta V)\) never exceeded 42 ml, which was generally well within the physiological range for these animals, and the rate of diastolic stretch (range, 0–220 ml/sec) never exceeded that which might occur during early diastolic filling of the normal in situ ventricle. In five of seven studies, stretch-response data were also obtained with \( V_i \) set to 10 or 30 ml, again chosen to avoid overdistension at peak stretch volume.

Measurements of the absolute refractory period were obtained as the ventricle was constrained to beat isovolumetrically with the volume set to the value of \( V_i \) used in the electromechanical stimulation protocol. After a drive of eight paced beats with a cycle length of 500 msec, a single programmed extrastimulus of 10 mA square wave current (2 msec) was administered. The initial coupling interval of the extrastimulus was 250 msec. The coupling interval was then reduced in decrements of 10 msec until failure to capture was observed. The coupling interval was then increased by 2-msec increments until capture was achieved. The absolute refractory period was defined as the longest coupling interval that failed to capture the ventricle at 10 mA. Previous studies demonstrate that this measurement of refractoriness is linearly related to the monophasic action potential duration at 90% repolarization, as measured by a contact electrode catheter.

At the completion of each study, the left ventricle was carefully trimmed, blotted dry, and weighed. The mean weight was 146±22 g (range, 119–180 g).

Data Acquisition

The ventricular electrogram, pressure, volume, and dP/dt were recorded on a multichannel recorder (model TA 2000, Gould). Data were also digitized on line at 500 Hz by a 12-bit analog-to-digital converter (Labmaster TM-100, Scientific Solutions, Solon, Ohio) interfaced with the digital computer. The digitized data were displayed in real-time on the video monitor and stored on an optical disc (Laser-Stor Optical Subsystem, Storage Dimensions, Los Gatos, California) for subsequent data analysis. The initial hemodynamic data were collected as a minimum of 5 consecutive steady-state beats in paced rhythm. During the electromechanical stimulation protocol, values of \( V_i, \Delta V, \Delta t \), and stretch duration were entered from the computer terminal, and a minimum of 20 control and stretch sequences was recorded for each experimental condition.

Data Analysis

The relation between left ventricular end-diastolic pressure \( (P_{ed}) \) and volume \( (V_{ed}) \) was analyzed by fitting pressure-volume pairs obtained over the physiological range to an exponential equation of the form:

\[
P_{ed} = \alpha \cdot e^{\beta (V_{ed})} + C
\]

(1)

where the fitting parameters \( \alpha, \beta, \) and \( C \) were determined by a standard nonlinear regression technique. End diastole was considered to occur at the time of the peak R wave of the ventricular electrogram.

To characterize the systolic performance of these ventricles independent of load, the slope and volume-axis intercept of the peak left ventricular isovolumetric pressure-volume relation were computed by the least-squares linear regression method. This relation can be expressed as

\[
P_{max} = E_{max} \cdot (V - V_o)
\]

where \( P_{max} \) is the peak left ventricular isovolumetric pressure, \( V \) is the volume, \( E_{max} \) is the slope, and \( V_o \) is the volume-axis intercept.

The stretch-response data were computer-analyzed by using an algorithm that automatically detected the electrocardiographic QRS complex during the 2,000-msec response period. From the control sequences, the timing of ventricular escape complexes was determined relative to the electrical stimulus of the final priming stimulus (\( t=0 \) in Figure 2). The longest time interval that excluded 95% of the ventricular escape complexes \( (t_{95}) \) was then determined using all control sequences obtained at a given \( V_i \) value. An SIA was defined as an electrocardiographic QRS complex after a stretch that occurred at a time when there was at least 95% confidence that it was not a ventricular escape complex (i.e., earlier than \( t_{95} \)). When the \( t_{95} \) point exceeded \( \Delta t + 500 \) msec, we arbitrarily used a cutoff of \( \Delta t + 500 \) msec since SIAs were found to occur 159±64 msec after the onset of active stretch. The probability of an SIA was then computed for each experimental condition as the number of SIAs divided by the total number of stretch sequences. At least 20 stretch sequences were used for these probability determinations.

The relation between the intensity of the stretch \( (\Delta V) \) and the probability of precipitating an SIA \( (P_{SIA}) \) was fitted to a Boltzmann distribution using the equation:

\[
P_{SIA} = C_v + \left[ A \left( 1 + e^{m(\Delta V - \Delta V_{50})} \right) \right]
\]

where \( \Delta V_{50} \), \( A \), and \( C_v \) are fitting parameters with \( \Delta V_{50} \) representing the amount of stretch resulting in a 50% probability of initiating an SIA. This analysis was performed by using a nonlinear-regression
approach with an iterative procedure to determine the various fitting parameters. The convergence criterion used for this iterative procedure was a change of less than 0.1% for all parameters.

Statistical Methods

The results of all experimental variables are expressed as mean±1 SD unless otherwise specified. Paired comparisons were performed by nonparametric techniques (Wilcoxon matched-pairs test). A value of \( p < 0.05 \) was considered statistically significant.

Results

Diastolic Compliance

The relation between end-diastolic pressure (abscissa) and volume (ordinate) was well fitted \( (r=0.982±0.021) \) by Equation 1. Individual regression curves are plotted in Figure 3 to illustrate variability among animals. Note that over the range of absolute volumes obtained at peak stretch under standard conditions (20–42 ml) the end-diastolic pressure generally remained 10–20 mm Hg, which is within the range commonly encountered in patients.

Systolic Performance

The relation between peak isovolumetric pressure and volume was linear over the range studied, as indicated by a mean correlation coefficient of 0.996±0.003. Positive values of \( \dot{V}_v \) were obtained in all animals, and the mean value of 4.8±3.8 ml was similar to those previously reported for the canine ventricle.\(^{33,34}\) \( E_{\text{max}} \) of this relation was considered a load-independent measure of the contractile state of the ventricular myocardium.\(^{33,34}\) The mean value of \( E_{\text{max}} \) obtained in our study was 3.6±0.7 mm Hg/ml, which is also within the range previously reported for the isolated canine ventricle.\(^{33,34}\) Thus, the contractile state of these ventricles after the isolation procedure was compatible with that previously reported.

Diastolic Stretch Elicits Arrhythmias

As derived from an average of 195±42 control sequences \( (n=7) \), the hearts remained electrically quiescent \( (t_{95}) \) for 699±82 msec after the final electrical stimulus of the priming period. In the experiment shown in Figure 4, \( t_{95} \) was 763 msec as indicated by the vertical dashed line. After the last electrically paced beat of the control sequence (left panel), no subsequent electrical activity (upper tracing) was observed for over 1,000 msec as the volume (lower tracing) was maintained constant at 20 ml. During this electrically quiescent period, the pressure (middle tracing) rapidly returned to the end-diastolic value of the final paced beat (9 mm Hg) without further pressure development. In the next cycle (right panel), left ventricular volume (lower tracing) was increased by 10 ml beginning 300 msec after the last priming stimulus. This volume change in early diastole resulted in an immediate 20–mm Hg increase in left ventricular pressure and altered the time course of relaxation (middle tracing) relative to the final paced beat of the control sequence. After 38 msec at peak stretch volume, a ventricular premature depolarization emerged on the electrocardiogram (see...
arrow, upper tracing). This early ectopic beat generated only a minimal increase in pressure.

In seven experiments, starting from a standard $V_i$ of 20 ml (Figure 5), volume changes in early diastole ($\Delta t=300$) smaller than 10 ml rarely resulted in ectopic beats. As the diastolic volume increment was increased, the probability of an SIA increased sharply. The volume change that resulted in a 50% probability of an SIA ($\Delta V_{50}$, Table 1) was 15.0±1.6 ml. There was no correlation between these $\Delta V_{50}$ values and either left ventricular weight ($r=0.320$) or body weight ($r=0.143$) of the donor dog. The probability of an SIA approached 100% as the volume increment was allowed to exceed the $\Delta V_{50}$ value. In six of the seven trials, a probability of 100% was achieved over the range of volume increments studied; a maximum probability of 85% was obtained under standard conditions in the remaining study, but SIAs could be elicited 100% of the time when stretch was initiated starting from higher volume (30 ml) in this ventricle.

**Effect of Preload**

In four ventricles, we increased $V_i$ from 20 to 30 ml, and in one of the less compliant ventricles, $V_i$ was decreased from 20 to 10 ml (Table 1). In all five cases, increasing $V_i$ sensitized the heart to SIAs. For example, in Figure 6, the $\Delta V_{50}$ was 12.4 ml when $V_i$ was 20 ml (solid circles), but when $V_i$ was increased to 30 ml, the $\Delta V_{50}$ was reduced to 6.7 ml. More strikingly, the maximum slope of the probability-volume curve became more than three times as steep (0.06 ml$^{-1}$ for $V_i=20$ ml vs. 0.22 ml$^{-1}$ for $V_i=30$ ml). The effect of a 10-ml change in the $V_i$ on the induction of SIAs is shown for all five ventricles in Figure 7 (open circles).

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**TABLE 1. Results of Electromechanical Stimulation in Seven Ventricles**

<table>
<thead>
<tr>
<th>Dog</th>
<th>$V_i$ (ml)</th>
<th>$P_{0.05}$ (mm Hg)</th>
<th>$P_{max}$ (mm Hg)</th>
<th>$\Delta V_{50}$ (ml)</th>
<th>Body wt (kg)</th>
<th>LV wt (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>1.8</td>
<td>42.0</td>
<td>15.3</td>
<td>23.7</td>
<td>119</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>5.6</td>
<td>54.0</td>
<td>16.2</td>
<td>24.3</td>
<td>132</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>9.0</td>
<td>94.5</td>
<td>11.9</td>
<td>29.5</td>
<td>180</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>2.3</td>
<td>31.3</td>
<td>20.5</td>
<td>26.3</td>
<td>155</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>10.3</td>
<td>66.8</td>
<td>15.2</td>
<td>34.1</td>
<td>165</td>
</tr>
<tr>
<td>6</td>
<td>20</td>
<td>1.4</td>
<td>45.3</td>
<td>13.7</td>
<td>22.4</td>
<td>127</td>
</tr>
<tr>
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<td>30</td>
<td>5.8</td>
<td>82.1</td>
<td>12.0</td>
<td>8.6</td>
<td>143</td>
</tr>
</tbody>
</table>

Results shown are at coupling interval of 300 msec and stretch duration of 50 msec. $V_i$, initial holding volume; $P_{0.05}$, end-diastolic pressure; $P_{max}$, peak isovolumetric pressure; $\Delta V_{50}$, volume increment resulting in 50% probability of stretch-induced arrhythmia; LV, left ventricular.

In all cases, $\Delta V_{50}$ decreased with increasing $V_i$ ($p<0.05$). Interestingly, the total ventricular volume associated with this 50% probability point ($V_i+\Delta V_{50}$) increased slightly ($p<0.05$) with increasing preload (solid circles). Thus, stretch activation is dependent on both $V_i$ and the $\Delta V$. Nevertheless, high preload appears to sensitize the ventricle to SIAs since smaller $\Delta V$s are required to elicit an arrhythmia starting from higher $V_i$.

**Effect of Electromechanical Coupling Interval**

In two of seven ventricles (dogs 1 and 6), the diastolic interval until an escape beat was long...
enough to compare a short (300 msec) and long (600 msec) coupling interval with the last priming stimulus. In both cases, ectopic beats were readily initiated with late-diastolic stretch. \( \Delta V_{50} \) at a standard \( V_i \) of 20 ml was similar for early and late diastole (15.3 vs. 13.2 ml for dog 1 and 12.0 vs. 11.9 ml for dog 6).

Transient stretch of 50-msec duration initiated early in systole (\( \Delta t \) of 50–100 msec) never provoked an arrhythmia in any study. In one ventricle, the effect of sustained stretch initiated shortly after the electrocardiographic QRS complex of the final paced beat (\( \Delta t = 100 \) msec) was systematically evaluated. This was done to exclude the possibility that the arrhythmias we observed with balloon dilatation were caused by friction between the expanding balloon and endocardial surface rather than by myocardial stretch. If balloon dilatation is completed while the ventricle is electrically refractory, then any arrhythmia provoked subsequently during sustained dilatation, at a time when the balloon volume is unchanging, must be due to myocardial stretch rather than friction. The results of this experiment are illustrated in Figure 8. A standard \( V_i \) (20 ml) was used, and \( \Delta V \) was adjusted to the minimum \( \Delta V \) (20 ml) that invariably generated SIAIs when stretch was initiated during early diastole (open circle in Figure 8, \( \Delta t = 300 \) msec). Early systolic stretch of short duration (50 msec) failed to provoke SIAIs (solid circle in Figure 8). However, early systolic stretches that were sustained well into diastole (350- and 500-msec duration) were nearly as effective (90% probability of SIA) as early diastolic stretch. We were also able to demonstrate that the arrhythmogenic effect of these prolonged dilatations was dependent on \( \Delta V \), yielding a relation analogous to Figure 5 (data not shown). Early systolic stretch of slightly shorter duration (250 msec) was substantially less arrhythmogenic, resulting in an intermediate probability (45%) of SIA. It should be noted that the time of deflation for the early systolic stretch of 250-msec duration exactly coincided with the time of deflation for early diastolic stretch under standard conditions; thus, in this experiment, early systolic stretch appears to have a desensitizing effect that can be almost totally overcome by maintaining stretch later into diastole.

**Characteristics of Stretch-Induced Arrhythmias**

When a diastolic volume change precipitated an SIA, it was usually a single ventricular premature depolarization. Although the ventricular premature depolarizations were multiformed in all studies, one or two morphologies generally predominated. The ectopic beats elicited by stretch were often relatively narrow in appearance (80–100 msec), although very broad activation patterns were also observed less frequently. Single ectopic beats were most common, but pairs and triplets were also provoked in all studies, and runs of ventricular tachycardia were precipitated in two studies. When ventricular tachycardia was elicited, the arrhythmia terminated during pacing of subsequent priming period; therefore, sustained ventricular tachycardia was never observed, and the rhythm never deteriorated into ventricular fibrillation. Figure 9 illustrates the first 2,000 msec of

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**FIGURE 7.** Plot of preload dependence of stretch-induced arrhythmias. The volume change (\( \Delta V_{50} \), open circles) and total absolute volume (\( V_i + \Delta V_{50} \), solid circles) required to precipitate stretch-induced arrhythmias with a probability of 0.5 are plotted for five ventricles as a function of the initial holding volume (\( V_i \)). As preload (\( V_i \)) was increased, \( \Delta V_{50} \) declined (\( p<0.05 \)) in all ventricles. However, \( \Delta V_{50} \) increased with \( V_i \) (\( p<0.05 \)).

**FIGURE 8.** Plot showing effect of early systolic stretch on arrhythmia induction. All data shown were obtained from the same ventricle with balloon dilatations of 20 ml initiated from an initial volume (\( V_i \)) of 20 ml. The probability of precipitating a stretch-induced arrhythmia is shown as a function of the stretch duration for stretches initiated 100 msec after the final pacing stimulus (solid circles). For comparison, the open circle shows the results for a 50-msec stretch duration beginning early in diastole (\( \Delta t = 300 \) msec). Although early systolic stretches of brief duration (50 msec) failed to elicit arrhythmias, ectopic beats were increasingly frequent as the duration that the balloon was maintained at peak stretch volume was increased. \( \Delta V \), change in volume used to elicit stretch.
an example of ventricular tachycardia after a 10-ml stretch initiated from a starting volume of 20 ml. The initial beat (arrow, upper tracing) occurs as the volume (lower tracing) is held at peak stretch volume for 50 msec; it has the typical narrow QRS morphology of an SIA and is followed by a run of wide complex tachycardia after the volume returned to \( V_0 \).

**Effects of Diastolic Stretch on Escape Beats**

In three hearts in which the ventricular escape beat of control sequences occurred late (\( t_{eg} > 1,500 \) msec), we were able to evaluate the effect of unsuccessful early diastolic stretches (\( \Delta t = 300 \) msec) on the timing of subsequent "spontaneous" escape beats. For this analysis, \( \Delta V_s \) that were 40–60% successful in precipitating an SIA were selected. In all three ventricles, stretch sequences that failed to elicit an SIA (no ectopic beat during the initial 500 msec after the onset of stretch) were associated with earlier appearance of the escape beat, on average, than the corresponding control sequences (1,398 vs. 1,702, 896 vs. 1,528, and 1,450 vs. 1,609 msec, respectively). Thus, stretches that did not precipitate an SIA shortened the average escape interval.

**Ventricular Refractoriness**

Under standard conditions, the absolute refractory period was 151±7 msec. With the relatively minor changes in preload (10 ml) used in our study, there was no significant change in absolute refractory period, and the observed changes never exceeded 5% in any study. In no instance was sustained ventricular tachycardia induced by the single programmed extrastimulus at any level of preload studied.

**Discussion**

**Diastolic Stretch Induces Arrhythmias**

The results of this study demonstrate that transient dilatation of a left ventricular intracavitary balloon during diastole predictably elicits premature ventricular depolarizations in the isolated perfused dog heart. This was true with dilatation early or late in diastole or when myocardial stretch was initiated in systole but maintained into diastole. These ectopic beats were induced during a time window in which ectopic beats occurred fewer than 5% of the time in the absence of ventricular dilatation. The arrhythmias elicited by transient stretch beginning 300 msec after the last priming stimulus occurred within the subsequent 200 msec, and spontaneous escape beats within 500 msec were virtually nonexistent. We found that a transient dilatation of appropriate amplitude (Figure 5) could nearly always induce a premature ventricular depolarization. The fact that these ectopic beats were temporally related to the dilatation as well as the smooth graded response between the amount of stretch and the probability of ventricular premature depolarization (Figure 5) reinforces the causal relation.

**Dilated Hearts Are More Vulnerable**

It is noteworthy that, as the ventricle was held at larger volume during the priming period, smaller diastolic dilatations were required to elicit a ventricular ectopic beat. Conversely, in one experiment in which \( V_i \) was reduced, larger diastolic dilatations were required to precipitate ventricular ectopic beats. Interestingly, this was true despite the fact that steady-state changes in volume load had minimal or no effect on electrophysiologic properties as judged from measurements of absolute refractory period. These results are consistent with the concept that dilated ventricles are more susceptible to the arrhythmogenic effect of acute stretch.

The question arises as to the exact nature of this mechanically induced electrical activity. Although pressure and volume changes are mechanically linked, the induction of arrhythmias appeared to correlate poorly with pressure. Indeed, end-diastolic pressure-volume relations illustrated in Figure 3 demonstrate that the ventricles in the present studies...
had variable degrees of passive stiffness. As a result, a given $\Delta V$ would give a relatively small pressure change in the highly compliant ventricles but a relatively large pressure change in the stiffer ventricles. However, in all experiments with a standard $V_i$ of 20 ml, $\Delta V$ between 12.6 and 16.8 ml resulted in SIAs 50% of the time (Table 1). Thus, arrhythmia induction correlates much better with $\Delta V_s$ than with pressure changes. Furthermore, since ventricles held at low $V_i$ required larger $\Delta V_s$ than dilated ones (open circles, Figure 7), the question arises whether arrhythmia induction correlates with absolute volume. To test this hypothesis, we plotted the total ventricular volume ($V_i+\Delta V_{50}$) associated with induction of ectopic beats 50% of the time as a function of $V_i$ (solid circles, Figure 7). In all experiments with standard $V_i$ of 20 ml, arrhythmias occurred when total volume was abruptly increased to between 32 and 36 ml. However, the total volume required to trigger the arrhythmia consistently increased ($p<0.05$) with increasing $V_i$. This suggests the possibility that adaptation to high sustained preload occurred.

The absolute pressure and volume were generally well within the physiologic range of these ventricles. Furthermore, the pressure at the time of peak stretch never exceeded the range of pressures normally encountered in the in situ ventricle. As can be seen from the passive end-diastolic pressure-volume relations (Figure 3), total volume of up to 40 ml resulted in clinically relevant end-diastolic pressure (<20 mm Hg) in five of seven ventricles. In the two ventricles with the poorest compliance, the end-diastolic pressure occurring with total ventricular volume of 40 ml was clearly elevated; nevertheless, their arrhythmic response to the diastolic volume increments was similar to the more compliant ventricles. It is unlikely, therefore, that these results can be attributed to overdistension of the ventricular chamber.

**Stretch-Activated Channel Hypothesis**

Our hypothesis regarding the cellular mechanism by which SIAs are generated is diagrammatically illustrated in Figure 10. The existence of stretch-activated channels has been recently reported in neonatal rat myocytes. These channels appear to have a conductance near 100 pS and a reversal potential ($E_s$ in Figure 10) of −30 to −40 mV. Thus, as indicated in Figure 10, activation of such channels during the action potential plateau (point A) would generate an outward repolarizing current, which would shorten the action potential duration (tracing 1), as observed in previous studies of isolated myocardial tissue. Conversely, stretch late during the action potential at potentials more negative than reversal potential (points B) would yield an inward or depolarizing current, which would prolong the action potential duration as observed by Lab40 in amphibian myocardium. If activation occurs after the action potential (point C), a depolarizing current is produced, which results in an afterdepolarization (tracings 3 and 4). This depolarization may reach threshold potential ($E_t$ in Figure 10) immediately, in which case an ectopic beat would be elicited (tracing 3), or may make the escape beat occur earlier in diastole (tracing 4). The presence of such afterdepolarizations with stretch of cardiac muscle has been observed with action potential recordings by micropettes in cardiac tissue and contact electrodes in whole hearts.

According to this hypothesis, as the volume of the ventricles is increased, more stretch channels would become activated. When enough stretch channels are activated during diastole so that the inward currents exceed the outward currents, depolarization results. When the depolarization reaches the threshold potential, an ectopic beat results. Furthermore, as the net outward repolarizing potassium currents decline during diastole, it is likely that progressively less stretch-activated inward current is required to reach the threshold potential. Although this is compatible with our limited observation in two animals that arrhythmias could be provoked with slightly smaller amounts of stretch later in diastole than early in diastole, additional studies are required to ascertain the precise relation between inducibility and electromechanical coupling interval. Finally, subthreshold stretches may elicit an inward depolarizing current that fails to reach threshold immediately. This inward current, however, could cause a latent
pacemaker to reach threshold sooner.\textsuperscript{41} This would seem to be a plausible explanation for our observation that escape beats occurred earlier when stretches did not directly elicit an SIA.

Finally, it is also possible that mechanoelectrical transduction is mediated by processes other than stretch channels. For example, stretch might alter the cellular cytoskeleton to mediate the release of a second messenger (e.g., calcium),\textsuperscript{42–44} which ultimately leads to a depolarization exceeding threshold. Indeed, studies using the photosensitive protein aequorin as an intracellular calcium indicator have shown that changes in cardiac muscle length can be associated with changes in intracellular calcium transients\textsuperscript{42,44,45} and concomitant action potential characteristics.\textsuperscript{45} Satisfactory answers to these questions will require more detailed investigations at the cellular and single-channel level.

**Potential Clinical Significance**

It is remarkable that patients with globally dilated ventricles or regional scars with dyskinesis frequently have serious ventricular arrhythmias and are vulnerable to sudden death.\textsuperscript{3–7} Based on the results of our study, it is distinctly possible that abnormal loading conditions and myocardial stretch, which are a common feature of these patients, may play an important role in arrhythmogenesis in this setting. In our study of normal well-perfused isolated canine ventricles, diastolic stretch readily precipitated single ventricular premature depolarizations, pairs, and triplets, and occasional runs of ventricular tachycardia. Under conditions in which ventricular tachycardia compromises cardiac output and coronary perfusion, it is expected that this could deteriorate into ventricular fibrillation. Furthermore, the extensive fibrosis and scarring observed in many diseased hearts would increase the vulnerability of such patients to reentry tachyarrhythmias once a stretch-induced ectopic beat was initiated.\textsuperscript{8–10}

The transient diastolic stretch produced by the servopump system in our study might be analogous to the clinically relevant situation of infarcted scars that frequently exhibit “systolic” bulging.\textsuperscript{46} Because the activation of scarred myocardium is frequently slow,\textsuperscript{9} the tissue in the scarred region could still be in electrical diastole at the time it is stretched even though the noninfarcted part of the ventricle is in systole. Such marked systolic distension during electrical diastole could elicit electrical activation in the scarred tissue. Because conduction in this region might also be slow, propagation to the normal myocardium might be delayed enough such that the surrounding normal myocardium would no longer be electrically refractory, and a ventricular premature depolarization would result. Another situation in which diastolic stretch might occur in the clinical situation is the compensatory pause of a ventricular premature depolarization. This pause results in a prolonged period of diastolic filling, which leads to an increased ventricular volume. Mechanoelectrical transduction in this situation might be an adaptive mechanism to prevent overdistension but would result in a ventricular couplet. Lastly, and perhaps most importantly, it is possible that the rapid ventricular distension that occurs during each cardiac cycle during early diastolic filling could be the trigger of SIAs in dilated ventricles. In our study, a threshold level of stretch had to be exceeded before such arrhythmias occurred. As the volume to which the ventricle was conditioned was experimentally increased, $\Delta V$ required to trigger an ectopic beat was greatly reduced. Thus, in the ejecting heart, the volume that triggers arrhythmias might be exceeded during early diastolic filling if the operating volume of the ventricle is sufficiently large. Although the early diastolic dilatation in our experiments was not exactly analogous to normal ventricular filling, the timing, amount, and rate of volume expansion were in point of fact quite similar to what might occur in the in situ ejecting heart.

It has recently been shown that in chronically infarcted ventricles volume loading increases inducibility of sustained tachyarrhythmias.\textsuperscript{32} However, we do not know how chronic global dilatation, humoral factors (e.g., catecholamines and other hormones), metabolic conditions (e.g., hypoxia or ischemia), electrophysiological conditions (e.g., heart rate), electrolytes (e.g., hypokalemia or hypermagnesemia), or pharmacologic agents (e.g., antiarrhythmic agents) influence SIAs. These factors are likely to influence arrhythmogenesis in patients with severe congestive heart failure, who are the patients at highest risk of serious ventricular arrhythmias.\textsuperscript{3–7}

**Comparison With Other Studies of Mechanoelectrical Feedback**

It is interesting to note that several other studies of isolated canine ventricles have failed to demonstrate an important mechanoelectrical feedback effect in normal myocardium.\textsuperscript{29,30,32} For instance, Calkins et al\textsuperscript{30} recently found that a twofold increase in end-diastolic volume resulted in minimal changes in absolute refractory period and local activation time with no change in monophasic action potential duration, overall dispersion of refractoriness, ventricular fibrillation threshold, or inducibility of ventricular tachyarrhythmias. The findings in the study of Lerman et al\textsuperscript{29} were similar. We also found that the ventricular refractoriness and inducibility of tachyarrhythmias with a limited programmed electrical stimulation protocol was not influenced significantly by steady-state increases in volume load. Our results demonstrating that arrhythmias can be readily and predictably induced by transient stretch need to be reconciled with these other studies. The main difference between our study and these earlier ones is that our study involved transient ventricular dilatation, as opposed to the steady-state conditions prevailing in the other studies. We were able to demonstrate in our comparison of data obtained at low ($V_l = 20$ ml) and high ($V_l = 30$ ml) volume that the ventricle under-
goes an adaption to high preload. Such adaptation might be particularly important in the studies of Calkins et al\textsuperscript{30,32} and Lerman et al\textsuperscript{29} in which much larger ventricular volumes were used and may explain why steady-state increases in ventricular volume (as opposed to the transient volume changes used in the present study) resulted in relatively minor changes in electrophysiologic properties and inducibility of ventricular tachyarrhythmias. Our method of arrhythmia induction with a mechanical stimulus is quite different from the standard programmed electrical stimulation protocols used by other investigators. Our method is more analogous to earlier studies of mechanoelectrical feedback in isolated cardiac tissue in which abrupt changes in muscle length during the action potential were observed to influence action potential duration.\textsuperscript{22,40} Despite the methodologic differences, we also did not find that sustained increase in preload enhanced the inducibility of ventricular tachyarrhythmias in normal myocardium.

**Potential Limitations**

Although it has been shown that the balloon conforms very closely to the geometry of the ventricular cavity,\textsuperscript{37} it is possible that slippage of the balloon over the inner ventricular surface might possibly produce some friction. Indeed, it was a major concern that friction between the intracavitary balloon and the ventricle at the time of balloon dilatation might be a source of artifact in these experiments. To address this important issue, the effect of early systolic stretch of progressively longer duration was evaluated. When the balloon was actually in the process of inflation during early systole, the balloon–ventricular surface interaction (or myocardial stretch for that matter) could not result in a ventricular premature depolarization because the ventricle was electrically refractory. Thus, a brief balloon inflation (50 msec) during early systole never elicited an ectopic beat (Figure 8). Ectopic beats were readily elicited, however, if the balloon remained inflated at constant volume into diastole. The ectopic beats that were provoked in this manner obviously occurred at a time when the balloon volume was static and when friction between the balloon and inner surface of the ventricle was minimal or absent. We further found that with prolonged stretches originating early in systole, the probability of inducing an ectopic beat was predictably dependent on the amount of stretch, yielding a relation analogous to Figure 5 (data not shown). Thus, we can be quite confident that these ectopic beats were induced by myocardial stretch rather than by friction.

We also wish to point out that there are obvious limitations in the use of “normal” ventricles in a study of arrhythmogenesis, because most life-threatening ventricular arrhythmias occur in patients with diseased ventricles in the clinical setting. Nevertheless, we believe that our findings apply to chronically infarcted or myopathic ventricles as well, in which it is likely that the abnormal myocardium provides a more suitable substrate for reentry tachyarrhythmias.\textsuperscript{8–10}

Lastly, our definition of SIA may seem a bit arbitrary in light of our findings in the three ventricles with the longest ventricular escape times. In these three ventricles, we were able to demonstrate that balloon dilatations in early diastole that failed to produce an ectopic beat within the first 500 msec after the mechanical stimulus shortened the average ventricular escape time relative to control. We speculate that myocardial stretch may produce an afterdepolarization that fails to reach threshold potential during the stretch, but this may result in the membrane potential reaching threshold earlier as shown in Figure 10 (tracing 4). Although this is our preferred interpretation of these data, the possibility that such beats represent delayed ventricular premature depolarizations cannot be excluded.

In summary, our study provides evidence of an important mechanoelectrical feedback effect in isolated normal ventricle. Appropriately timed myocardial stretch can induce ventricular ectopic beats that can trigger more serious arrhythmias, including ventricular tachycardia. The dilated ventricle is especially susceptible to the development of such SIAs. We suspect that patients with globally dilated or regionally dyskinetic ventricles may be especially prone to the development of ventricular arrhythmias by this mechanism. Interventions that alleviate the abnormal loading conditions in such patients may have a favorable effect on the mortality associated with ventricular arrhythmias in this setting.\textsuperscript{47} Moreover, a better understanding of mechanoelectrical feedback and its role in arrhythmogenesis may eventually lead to the development of a new class of pharmacologic agents that prove to be efficacious in the treatment of serious ventricular arrhythmias associated with severe heart failure.

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