Demand ischemia, induced by rapid pacing in the presence of critical coronary stenosis, shifts the diastolic pressure-volume curve upward (3, 5–7, 21–23). The pathophysiological mechanism of this shift is not yet established, although several mechanisms have been proposed, generally relating to the level of Ca$^{2+}$ dynamics within the sarcomere. It is possible that agents that affect Na$^+$/Ca$^{2+}$ exchange, such as lidocaine, a class 1b-type Na$^+$-channel blocker that decreases intracellular Na$^+$, could affect the diastolic pressure-volume relationship because of indirect effects on intracellular Ca$^{2+}$. Lidocaine is a drug widely used to treat arrhythmias in patients with myocardial ischemia. We studied the effects of lidocaine on diastolic dysfunction associated with demand ischemia. We compared diastolic (as represented by the shift in the diastolic pressure-volume relationship) and systolic function during demand ischemia before and after lidocaine injection. We created demand ischemia in pigs before and after administering lidocaine (5 mg/kg) in eight open-pericardium anesthetized pigs. Demand ischemia was induced by constricting the left anterior descending coronary artery and then pacing at 1.5–1.8 times the baseline heart rate for 1.5–3 min. Hemodynamics were recorded during baseline, demand ischemia, baseline after lidocaine injection, and demand ischemia after lidocaine. Lidocaine did not affect systolic function or the time constant of isovolumic relaxation, but it increased the upward shift of the diastolic pressure-volume curve during demand ischemia compared with the increase that occurred before lidocaine was administered. This result suggests that lidocaine could aggravate diastolic dysfunction in patients with ischemic heart disease.

**METHODS**

All animal work was approved by the University of California, San Francisco, Committee on Animal Research.

**Surgical Preparation**

The eight female pigs (40.7 ± 2.40 kg) used in this study were premedicated with a subcutaneous injection of ketamine (20 mg/kg) mixed with xylazine (2 mg/kg). Anesthesia was achieved using an intravenous injection of α-chloralose (100 mg/kg), fentanyl (1 µg/kg), and pancuronium bromide (4 mg). Tracheal intubation was performed and respiration maintained using a ventilator (Harvard Apparatus Respiratory Pump Speed Control, Bodine Electric, Chicago, IL). Additional doses of α-chloralose, fentanyl, and pancuronium bromide were given periodically to maintain general anesthesia. The pig was placed in the supine position, and a median sternotomy was performed. The pericardium was opened widely to expose the left anterior descending artery (LAD), the left ventricular (LV) apex, and the left atrial (LA) appendage. A pericardial cradle was made by suturing the edges of the pericardium to the skin surrounding the sternotomy.

**Instrumentation**

LV and LA pressures were measured with high-fidelity 5-F pressure micromanometer catheters (Millar Instruments) inserted into the LV and LA via the LV apex and the LA appendage (Fig. 1). These catheters were warmed at 37°C in a water bath for 12 h before use; bench tests in our laboratory showed that these catheters drift <0.5 mmHg/5 h after being stabilized in this manner.

To measure LV volume, a 7-F, eight-electrode, single-field conductance catheter (Webster Laboratories) was inserted in the LV through the LV apex with the tip electrode above the aortic valve and with the most proximal electrode at the apex. The conductance catheter was connected to a signal processor (Stitching Leycom-Sigma-5DF), which converts the conductance signal into volume (2). The conductance catheter and signal processing electronics are designed to have the catheter introduced through the aortic valve, not the apex. To obtain correct volume results with the catheter introduced through the apex, we used a custom-made adapter that reversed the electrode sequence of the catheter. The catheter was checked for proper positioning by comparing the individual segment signals. Because we were interested in vol-
ume changes and not absolute volumes, we based our analysis on uncorrected total conductance volume signals (4).

To confirm the absence of impaired regional systolic function when creating a critical coronary stenosis, and to assess the pressure-segment length relationship before and after creating demand ischemia, pairs of ultrasonic crystals were implanted in the areas perfused by the LAD and left circumflex coronary artery (LCX). The crystals were implanted parallel to the LV short axis and were positioned in the circumferential plane. The distance between each pair of crystals was ~1.5 cm. The crystals were connected to a sonomicrometer (Triton Technology).

To measure the coronary blood flow in the LAD, the short segment of the LAD just distal to the bifurcation of the first diagonal branch was carefully dissected and a transit-time ultrasonic flow probe (Transonic Systems) was placed around the LAD.

All hemodynamic signals [LV pressure, LA pressure, LV volume, LAD coronary flow, electrocardiogram (ECG), and segment lengths in the areas perfused by the LAD and LCX] were monitored continuously on a multichannel oscillograph and digitized at 200 Hz with a personal computer. The peak rate of LV pressure development (dP/dtmax) was monitored throughout the experiment as an index of LV contractility.

To create a coronary stenosis on the LAD, an adjustable occluder (24, 28, 29) was placed around the LAD just proximal to the bifurcation of the first branch. The adjustable occluder consisted of a head made of metal and a body made of plastic; the head was designed like a screw, and the body was designed in a "C" shape to be placed around the vessel in a stable standing position.

To measure myocardial pH continuously, a pH sensor (Micro-combination pH Electrodes) was calibrated with the use of buffers with pH 4.0 and 7.0, and then a H⁺-selective polymer membrane pH electrode was inserted into the myocardium perpendicular to the surface of the myocardium in the region supplied by the LAD so that the tip of the sensor was firmly placed in the endocardium.

To pace the heart, electrodes were attached to the LA using a demand-type stimulator (Medtronic Pacing System Analyzer model 5309).

To produce a range of pressures and volumes to measure end-diastolic pressure-volume relationships (EDPVR), an occlusion balloon catheter (8-F Fogarty venous thrombectomy catheter) was inserted through a femoral venous sheath into the inferior vena cava.

The pigs were given intravenous heparin (5,000 U) as an anticoagulant after the instrumentation had been completed.

Protocol

The protocol for each experiment consisted of four conditions: baseline, demand ischemia, baseline after lidocaine injection, and demand ischemia after lidocaine injection. During each condition, we obtained the LV pressure-volume loops and the EDPVR and end-systolic pressure-volume relationships (ESPVR) during vena cava occlusion. We then compared the shift of the diastolic segments of the pressure-volume loops and the EDPVR and ESPVR from baseline to demand ischemia (the shift produced by demand ischemia) and from baseline after lidocaine injection to demand ischemia after lidocaine injection (the shift produced by demand ischemia after lidocaine injection).

After instrumentation was completed and a hemodynamic steady state was achieved, we measured the blood conductiv-
ity \((p)\) to convert conductance into volume. \(p\) was also measured before each data recording episode.

LV pressure, LA pressure, LV volume, ECG, LAD coronary flow, and the segment lengths in the areas perfused by the LAD and LCX were recorded with the respirator stopped at end expiration. Next, preload was reduced by inflating the balloon in the inferior vena cava during data acquisition, and data were recorded during the transient phase of the vena cava occlusion when pressure was falling. We analyzed EDPVR and ESPVR by combining the data collected during the steady-state and declining phases of the vena caval occlusion. Just after the hemodynamic data were recorded during baseline for over 30 s, we printed out the LV pressure-volume loop and the EDPVR from the personal computer used to record the data.

To create demand ischemia, we produced a stenosis by constricting the adjustable vessel occluder on the LAD just proximal to the bifurcation of the first diagonal branch to reduce the peak anterograde flow velocity in the distal LAD by \(-30\%\) (27) while preserving the rest level of systolic shortening of the segment perfused by the LAD. This degree of reduction in coronary flow corresponds to a 75–90% lumen stenosis (9).

After the LAD stenosis was adjusted to reduce the peak coronary flow velocity by \(-30\%\), we paced the heart at 1.5 times the resting heart rate for 1.5 min. We recorded hemodynamic variables immediately after cessation of the rapid pacing and then released the occlusion of the LAD.

To compare the EDPVR during demand ischemia with that during baseline, we printed out both the LV pressure-volume loop and the EDPVR during demand ischemia and compared them with those obtained during baseline. We drew the regression lines for both EDPVRs, regarding the maximal end-diastolic volume points on the lines as the end points, and then defined the upward-shift index (U) as end-diastolic pressure-volume relationship between baseline and demand ischemia.

The pacing rate (up to 1.8 times the resting heart rate) for the same duration as before. If neither occluding the LAD a little more tightly nor increasing the rate of rapid pacing to 1.8 times the resting heart rate produced an upward shift, we extended the duration of rapid pacing to 5 min. We repeated this procedure until an upward shift of the EDPVR was observed.

Table 1 shows that we obtained an upward shift in EDPVR on the first try in one pig (no. 704), the second try in three pigs (nos. 707, 709, and 711), and the third (no. 713), fourth (no. 705), fifth (no. 703), and eighth (no. 706) try in one pig each. In three experiments (nos. 703, 705, and 706), we infused phentolamine (4 mg/kg) to keep peak systolic pressure \(<100\) mmHg. In one experiment (no. 706), \(\mathrm{dP}/\mathrm{d}t_{\text{max}}\) was \(<1,300\) mmHg/s during baseline, so we infused milrinone (900 \(\mu\)g) to keep \(\mathrm{dP}/\mathrm{d}t_{\text{max}} > 2,000\) mmHg/s. The baseline LAD flow before occlusion was 42.9 \(\pm\) 7.0 ml/min (mean \(\pm\) SE); LAD flow was reduced to 66.3 \(\pm\) 3.5% of baseline when we obtained the upward shift of the diastolic pressure-volume curve (Table 1). The baseline LAD heart rate was 90.5 \(\pm\) 15.5 beats/min, the pacing rate was 1.61 \(\pm\) 0.17 times the resting heart rate, and the pacing duration was 1.88 \(\pm\) 0.69 min when we obtained the upward shift of the diastolic pressure-volume curve during demand ischemia.

We waited for at least 10 min after recording the data for baseline demand ischemia to allow hemodynamics to stabilize while the LAD was occluded. We then administered 1% lidocaine (5 mg/kg iv). We waited at least 30 min after lidocaine injection before measuring postlidocaine baseline. We used the 5 mg/kg lidocaine dose because Matsumura et al. (18) have previously shown that lidocaine at the dose of 5 or 10 mg/kg neutralized the myocardial acidosis induced by partial LAD occlusion in dogs \(-30\) min after the occlusion, but that lidocaine at the dose of 10 mg/kg decreased systolic pressure. Therefore, use of the 5 mg/kg dose avoided the situation in which lidocaine impaired systolic pump performance.

Finally, we created the same level of stenosis as before lidocaine was administered, defined as the level of stenosis that reduced LAD flow by the same percentage as before. Next, we paced the heart at the rate that corresponded to the same multiple of the heart rate observed during baseline after lidocaine injection, for the same duration used to create demand ischemia before the lidocaine injection (Table 1). We recorded the hemodynamics and the LV pressure-volume loop and the LV EDPVR immediately after terminating pacing, as before.
Data Acquisition

During each episode, data were recorded for at least 30 s with the ventilator stopped at end expiration. The first seven beats of data (~5 s) were recorded in steady state to obtain steady-state hemodynamic variables, and at least 20 s were recorded during veno caval occlusion and release to obtain the EDPVR and ESPVR. We did not include the data recorded during veno caval release in our analysis. All hemodynamic data were digitized on line with a personal computer (Dell P-90) equipped with a 12-bit analog-to-digital converter (National Instruments N8-M10-64) using data processing software (LabView 3.1, National Instruments) at a sampling rate of 200 Hz. We analyzed the data using software developed in our laboratory. Premature ventricular contractions and the subsequent beats were excluded from the entire analysis.

Data Analysis

Hemodynamic variables in steady-state beats. Hemodynamic variables from steady-state beats were calculated as the mean of the variables for the first seven beats in each recording.

Stroke volume (SV) was calculated as

\[ SV = V_{ed} - V_{es} \]

where \( V_{ed} \) is end-diastolic volume and \( V_{es} \) is end-systolic volume. End diastole was defined as the starting point of the rapid upstroke of dP/dt (~10% of dP/dt max). End systole was defined as the point of maximal systolic elastance, computed by the iteration method of Kono et al. (13).

Stroke work (SW) was calculated as

\[ SW = \int P \, dV = \int P \, dV/dt \, dt \]

where \( P \) is LV pressure and \( V \) is LV volume. The integral is over one cardiac cycle, from end diastole to the end diastole of the next beat.

Segment function was analyzed using percent systolic shortening (SS). SS of each segment length was calculated as

\[ SS = \frac{ \max - \min }{ \max } \times 100\% \]

where \( \max \) is maximal segment length and \( \min \) is minimal segment length.

The time constant of left ventricular isovolumic relaxation \( \tau \) was estimated by fitting the function \( P = P_0 e^{-t/\tau} \) to the isovolumic relaxation period with the linear regression (36)

\[ \ln P = -t/\tau + \ln P_0 \]

where \( t \) is time after minimum dP/dt (dP/dt min) and \( P_0 \) is the estimated LV pressure at the time of dP/dt min. The end of the isovolumic relaxation period was defined as the time at which LV pressure dropped below LA pressure.

Pressure-volume loop of single beats. To examine the shift of the LV pressure-volume loops, a single pressure-volume loop during steady-state beats for each episode was plotted and

<table>
<thead>
<tr>
<th>Table 1. Conditions producing upward shift in diastolic pressure-volume curve</th>
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<tbody>
<tr>
<td><strong>Experiment</strong></td>
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<tr>
<td><strong>No. and Assistant Drug</strong></td>
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<tr>
<td>703 (with PE)</td>
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<tr>
<td>704</td>
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<td>705 (with PE)</td>
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<td>711</td>
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<td>713</td>
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<tr>
<td>Mean</td>
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| Values indicated by asterisks were used to compute summary statistics (means ± SE) for data recorded before lidocaine injection. Values in parentheses after left anterior descending artery (LAD) flow postocclusion data indicate ratio of postocclusion to preocclusion flow (%), and values in parentheses after pacing rate data indicate multiple of resting heart rate (HR) at which pacing occurred (see text for details). PE, phenylepinephrine; Mil, milrinone.
Diastolic function. The LV EDPVR was defined as the end-diastolic pressure-volume points obtained during vena caval occlusion. First, end-diastolic pressure-volume points for each of the four episodes of the eight experiments were plotted and visually compared in each pig. We then conducted a linear regression of end-diastolic pressure against end-diastolic volume (Fig. 2). The shift of the EDPVR from baseline to demand ischemia was quantified by an upward-shift index, U, as the end-diastolic pressure during demand ischemia minus the pressure during baseline at the largest end-diastolic volume common to both conditions (Fig. 2A). We also computed a rightward-shift index, R, as the largest end-diastolic volume during demand ischemia minus the largest end-diastolic volume during baseline (Fig. 2B).

Systolic function. To define the LV ESPVR, we applied linear regression to the LV end-systolic points of the pressure-volume loops during vena caval occlusion. The linear ESPVR was defined as

$$P_{es} = E_{es}(V_{es} - V_d)$$

where $P_{es}$ is the end-systolic pressure, $V_s$ is the volume-axis intercept (26), and $E_{es}$ is the end-systolic elastance. $E_{es}$ and $V_d$ were estimated by use of the iteration procedure described by Kono et al. (13).

As another index of LV contractile performance, we used the $dP/dt_{max}$-$V_{es}$ relationship (8, 10, 19). The $dP/dt_{max}$ relationship is defined as

$$dP/dt_{max} = dE/dt_{max}(V_{es} - V_{dp/s})$$

where $dE/dt_{max}$ is the slope of the $dP/dt_{max}$-$V_{es}$ relationship and $V_{dp/s}$ is the intercept with the volume axis. The slope of the $SW-V_{es}$ relation is defined as

$$SW = M_{SW}(V_{es} - V_{SW})$$

where $M_{SW}$ is the slope of the $SW-V_{es}$ relationship and $V_{SW}$ is the intercept with the volume axis. Data for both relationships were fit with linear regression.

Statistics

To test for significant changes in the hemodynamic variables caused by demand ischemia and lidocaine injection, we used two-way repeated-measures ANOVA. This design permitted us to test three hypotheses about each variable: 1) demand ischemia does not affect the variable when we control for the presence of lidocaine; 2) lidocaine does not affect the variable when we control for ischemia; and 3) the effects of ischemia are different, depending on whether lidocaine is present (the interaction effect). We compared the upward shift from baseline to demand ischemia with that from baseline after lidocaine injection to demand ischemia after lidocaine injection and compared the rightward shift from baseline to demand ischemia with that from baseline after lidocaine injection. All comparisons were done with SigmaStat Version 2.0 (Jandel Scientific). Differences were considered to be significant when $P < 0.05$.

RESULTS

Hemodynamic Variables

During demand ischemia, LV end-diastolic pressure ($P < 0.01$), $dP/dt_{min}$ ($P < 0.01$), $V_{es}$ ($P = 0.02$), $V_{es}$ ($P = 0.03$), maximal LA pressure ($P < 0.01$), and $r$ ($P < 0.01$) increased, whereas LV systolic performance fell, as evidenced by a decrease in $P_{es}$ ($P < 0.01$). Maximal LV pressure ($P < 0.01$), $dP/dt_{max}$ ($P < 0.01$), $SV$ ($P = 0.03$), $SW$ ($P = 0.04$), $dE/dt_{max}$ ($P < 0.01$), and myocardial pH ($P < 0.01$) decreased (Table 2; P values are for the main effect of demand ischemia in the 2-way ANOVA). Consistent with reports of previous researchers (24, 27–29) regarding the hemodynamic consequences of demand ischemia in pigs, the LV diastolic pressure increased, whereas the systolic values decreased, during demand ischemia.

Lidocaine did not change the hemodynamic variables significantly, after we controlled for the presence of ischemia (see $P$ values for main effect of lidocaine in 2-way ANOVA, Table 2). This result is consistent with earlier work by Matsumura et al. (18).

Lidocaine had a significant interaction effect with demand ischemia for LV end-diastolic pressure ($P = 0.04$) and myocardial pH ($P < 0.01$). The increase in LV end-diastolic pressure during demand ischemia was greater in the presence of lidocaine (Table 2). As expected (12, 18), lidocaine blunted the change in myocardial pH that occurred during demand ischemia (Table 2). (This result is not surprising, because H* reduces Ca$^{2+}$ sensitivity of myofilaments so that for any level of diastolic Ca$^{2+}$, force will be higher at higher pH.) These results suggest that lidocaine worsens the effects of demand ischemia on diastolic, but not systolic, function.

Changes in Single Loops of LV Pressure-Volume Curve

We recorded upward shifts during demand ischemia both before and after lidocaine injection in single loops of LV pressure-volume curves (Fig. 3). The magnitude of the upward shift created by demand ischemia was significantly greater with lidocaine (7.01 ± 3.3 vs. 4.31 ± 1.3 mmHg, $P < 0.05$) (Fig. 4) than that created by demand ischemia alone. Demand ischemia induced an upward shift in all experiments, regardless of the presence or absence of lidocaine.

Determinants of Shift of EDPVR

The end-diastolic pressure-volume curve shifted upward with demand ischemia both before and after lidocaine (Fig. 5). The upward shift index, $U$, without lidocaine was 3.79 ± 1.43 mmHg (range: 2.20 to 5.90 mmHg), and that after lidocaine injection was 5.90 ± 2.18 mmHg (range: 2.84 to 8.82 mmHg) (Fig. 6A). The upward shift in the EDPVR with demand ischemia was significantly greater ($P = 0.038$) in the presence of lidocaine.

The magnitude of the upward shift index, $U$, was significantly correlated with baseline contractility, quantified as $dP/dt_{max}$ ($r = 0.74$, $P = 0.036$). This result is
consistent with earlier work (21, 29) showing that the higher baseline contractility, the greater the upward shift with demand ischemia.

Lidocaine also affected the rightward shift of the EDPVR that accompanied demand ischemia (P = 0.039). Without lidocaine, the index of rightward shift of the EDPVR curve, R, shifted rightward with demand ischemia by $3.71 \pm 5.87$ ml (range: $-5.75$ to $12.1$ ml); after lidocaine, demand ischemia was associated with a leftward shift, quantified as $R = -3.19 \pm 6.28$ ml (range: $-13.1$ to $4.77$ ml) (Fig. 6B).

Determinants of LV Contractility

The effects of lidocaine on the response to ischemia were reflected in diastolic, not systolic, function. $E_{es}$, $dE/dt_{max}$, and $M_{SW}$ decreased significantly during demand ischemia ($P = 0.03$, $P < 0.01$, and $P < 0.01$, respectively) (Table 2), but the volume-axis intercepts of these three measures of systolic function, $V_{dP/dt\text{ }\text{pH}}$, $V_{dP/dt\text{ }\text{pH}}$, and $V_{SW}$ did not change significantly with ischemia. Lidocaine did not change any of these three indexes of LV contractility significantly or did not have a significant interactive effect with demand ischemia. Demand ischemia depressed systolic function; this effect was not modulated by the presence of lidocaine.

Myocardial pH

Myocardial pH in the territory made ischemic by LAD constriction (within 5 mm of the LAD $\sim 1$ cm distal to the vessel occluder) significantly ($P < 0.05$) decreased during demand ischemia (Table 2). Lidocaine had a significant interaction effect with demand ischemia ($P < 0.01$), meaning that the effects of demand ischemia on myocardial pH were different, depending on the presence or absence of lidocaine. Lidocaine reduced myocardial pH before demand ischemia and blunted the effect of demand ischemia on pH.

**DISCUSSION**

The primary finding of this study is that lidocaine, in doses small enough to avoid depression in systolic function, increases the upward shift in the diastolic pressure-volume curve produced by demand ischemia.

Several hypotheses have been proposed to explain the upward shift of the diastolic pressure-volume curve during demand ischemia: 1) increased diastolic Ca$^{2+}$-secondary to reduced sarcoplasmic reticulum ATPase activity (5, 11, 21); 2) increased diastolic Ca$^{2+}$-secondary to increased Ca$^{2+}$ influx from Na$^{+}$/Ca$^{2+}$ exchange in the setting of increased intracellular Na$^{+}$ due to ischemia; 3) increased diastolic Ca$^{2+}$-secondary to increased inward Ca$^{2+}$ current through L-type Ca$^{2+}$ channels; 4) no increase in diastolic Ca$^{2+}$, but impaired cross-bridge inactivation on an energetic basis (32); and 5) increased diastolic Ca$^{2+}$-secondary to stretch-activated channels (24, 28). The results of our experiments with lidocaine are inconsistent with the first two hypotheses and consistent with the last three hypotheses.

### Table 2. Hemodynamic variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Lidocaine Injection</th>
<th>After Lidocaine Injection</th>
<th>P Value</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Demand ischemia</td>
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</tr>
<tr>
<td>HR, beats/min</td>
<td>Baseline</td>
<td>Demand ischemia</td>
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<tr>
<td>LAD flow, ml/min</td>
<td>Baseline</td>
<td>Demand ischemia</td>
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<tr>
<td>$P_{es}$, mmHg</td>
<td>Baseline</td>
<td>Demand ischemia</td>
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<tr>
<td>$P_{es}$, mmHg</td>
<td>Baseline</td>
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<tr>
<td>$LVP_{max}$, mmHg</td>
<td>Baseline</td>
<td>Demand ischemia</td>
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<tr>
<td>$dP/dt_{max}$, mmHg</td>
<td>Baseline</td>
<td>Demand ischemia</td>
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<tr>
<td>$dP/dt_{min}$, mmHg</td>
<td>Baseline</td>
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<td>$V_{es}$, ml</td>
<td>Baseline</td>
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<td>$V_{es}$, ml</td>
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<tr>
<td>$V_{dP/dt\text{ }\text{pH}}$</td>
<td>Baseline</td>
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<td>$V_{dP/dt\text{ }\text{pH}}$</td>
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<td>$V_{SW}$, ml</td>
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<td>$V_{SW}$, ml</td>
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<td>Baseline</td>
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</table>

Variable values are means ± SE representing least-square means from 2-way repeated-measures ANOVA on 2 factors (demand ischemia and lidocaine injection); n = 8 pigs. $P_{es}$ and $P_{es}$, left ventricular end-diastolic and end-systolic pressure; $LVP_{max}$, maximal left ventricular pressure; $dP/dt_{max}$ and $dP/dt_{min}$, maximal and minimal LV contractility; $V_{es}$ and $V_{es}$, left ventricular end-diastolic and end-systolic volume; $SV$, stroke volume; $SW$, stroke work; $SS-LAD$ and $SS-LCX$, percent systolic shortening of LAD and left circumflex coronary artery; $t$, time constant for left ventricular isovolumic relaxation; $LAP_{max}$ and $LAP_{min}$, maximal and minimal left atrial pressure; $E_{es}$, end-systolic elastance; $V_{es}$, end-systolic volume; $M_{SW}$, slope of SW–$V_{es}$ relationship; $V_{dp/dt}$, volume-axis intercept of $dp/dt_{max}$–$V_{es}$ relationship; $M_{SW}$, slope of SW–$V_{dp/dt}$ relationship; $pH$, myocardial pH.
In support of persistence of Ca\(^{2+}\) from the previous systole as a mechanism of the upward shift, Kihara et al. (11) demonstrated that during 5 min of hypoxia, both free Ca\(^{2+}\) concentration and LV isovolumic pressure increased during diastole and decreased during systole. Authors (20) who support the residual cross-bridge interaction theory propose that a buildup of tissue metabolites such as H\(^+\) and Na\(^+\) due to decreased washout by coronary flow reduced the upward shift and increased the rightward shift of the diastolic pressure-volume curve during ischemia. These metabolites, as well as intracellular acidosis (induced by accumulated H\(^+\)), inhibit contractile activity by reducing the Ca\(^{2+}\) sensitivity of the myofilaments and thus induce contractile failure despite higher myoplasmic Ca\(^{2+}\). Lidocaine also reduces tissue metabolites such as Na\(^+\) and H\(^+\). There is also evidence that lidocaine reverses increases in cellular Ca\(^{2+}\) that occur during ischemia associated with ventricular fibrillation. Stefenelli et al. (25) subjected isolated rat hearts to 1 min of pacing-induced ventricular fibrillation and found that diastolic [Ca\(^{2+}\)] increased above the end-systolic [Ca\(^{2+}\)] of normal beats. Lidocaine reversed this effect; [Ca\(^{2+}\)] during fibrillation returned to the levels observed during baseline conditions, and the hearts converted to sinus rhythm. In the present experiments, however, lidocaine increased the upward shift and reduced the rightward shift of the diastolic pressure-volume curve.

There is good evidence from studies of isolated muscle (14, 34) that Na\(^+/\)Ca\(^{2+}\) exchange accounts for most of the sarcolemmal Ca\(^{2+}\) exchange [77% according to one
study (35)] and that this exchange is more related to the resting tension than to the sarcoplasmic reticulum-mediated Ca\textsuperscript{2+} flux. Resting tension increases when cardiac muscle is put in a low-Na\textsuperscript{+} or Na\textsuperscript{+}-free bath (14, 15) because there is a buildup of intracellular Ca\textsuperscript{2+} in exchange for the outward flux of Na\textsuperscript{+} driven by the Na\textsuperscript{+} concentration gradient. Conversely, lower levels of intracellular Na\textsuperscript{+} reduce the concentration gradient that drives Na\textsuperscript{+} out of the cell and Ca\textsuperscript{2+} into the cell via Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange. Thus intracellular Na\textsuperscript{+} accumulation is correlated both with Ca\textsuperscript{2+} levels and increases in diastolic pressure in isolated rat hearts (30, 31).

If the upward shift of the diastolic pressure-volume curve that accompanies demand ischemia was due to an increase in the background level of Ca\textsuperscript{2+} within the sarcomere, we would expect lidocaine to attenuate the effects of demand ischemia by blocking Na\textsuperscript{+} influx. We found that lidocaine had just the opposite effect. Thus our results are inconsistent with the hypothesis that the upward shift of the diastolic pressure-volume curve

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**Fig. 5.** End-diastolic pressure-volume relationships for all pigs.

**Fig. 6.** Lidocaine increases upward shift (A) and reduces rightward shift (B) of end-diastolic pressure-volume relationship. Symbols indicate results from individual pigs (n = 8).

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- Baseline without Lidocaine
- Demand Ischemia without Lidocaine
- Baseline after Lidocaine Injection
- Demand Ischemia after Lidocaine Injection
is due to an increase in the background level of Ca\(^{2+}\) within the sarcomeres during diastole.

Our results are consistent with, but do not prove, the stretch-activation hypothesis. In support of stretch activation of the myocardium as a mechanism, Shintani and Glantz (24) used an LV volume clamp to show that during demand ischemia, the LV diastolic pressure-volume curve did not shift upward without filling of the ventricle, i.e., without stretch of the myocardium during filling. According to this hypothesis, when the myocardium is ischemic, the sarcolemma and the sarcoplasmic reticulum may become more likely to release Ca\(^{2+}\) in response to stretch. The released Ca\(^{2+}\) increases actin-myosin interaction during diastole, resulting in the upward shift of the diastolic pressure-volume curve. Further support is that gadolinium, a stretch-activated channel blocker, attenuated the shift in the diastolic pressure-volume curve associated with demand ischemia (28).

**Limitations**

There are several limitations of this study worth considering. We found it difficult to create a stable model of demand ischemia in the anesthetized pig. The procedure used to create demand ischemia in pigs differs slightly from our previous procedure used to create demand ischemia in dogs (24, 28, 29). In the earlier experiments on dogs, we occluded the LAD until impaired segment systolic shortening was observed and then released the occluder slightly so that the stenosis had no detectable effect on segmental function. In preliminary experiments in pigs, however, occluding the LAD enough to impair segment systolic shortening often triggered ventricular fibrillation before the occluders could be slightly released, and the pig often died. The revised procedure we used to occlude the LAD in this study avoided this problem. Nevertheless, it often took several attempts to obtain an upward shift in the diastolic pressure-volume curve (Table 1). It is possible that there was some form of ischemic preconditioning caused by the repeated attempts to create the demand ischemia model. Nevertheless, among the episodes of data used in the analysis, the results were reasonably consistent.

The dose of lidocaine we used was selected to be small enough to avoid depression of systolic function, so there is some concern that we were not producing a substantial effect on the Na\(^{+}\) channel. The fact that we found changes in diastolic function, however, is evidence that the dose we used was adequate to produce physiological changes.

The data for myocardial pH during baseline before and after lidocaine injection are different (7.57 ± 0.02 vs. 7.47 ± 0.05, P < 0.01). Lidocaine was administered after data were collected from the first period of demand ischemia. Before lidocaine was administered, we waited at least 10 min for hemodynamic variables (pressures, heart rate, and coronary flow) to return to baseline levels (Table 2). Tissue pH did not return to control levels before lidocaine was administered. In addition, the increase in pH may have counteracted and overwhelmed the effects of reduced intracellular Ca\(^{2+}\) in our experiments because the increase in pH is associated with increased troponin sensitivity to Ca\(^{2+}\), which would lead to increased force for any given Ca\(^{2+}\) concentration. We do not know what effect, if any, these modest differences in baseline pH could have had on our results. It was clear, however, that the lidocaine blunted the effects of ischemia on changing pH.

The nature of the protocol required us to create several episodes of ischemia, which could have produced stunning or preconditioning. Either of these effects could have introduced artifacts in the second demand ischemia period, in which we administered the lidocaine. We sought to avoid this problem by waiting at least 40 min after the first demand ischemia episode before recording the postlidocaine baseline data. The fact that both diastolic and systolic function, measured as diastolic and systolic pressures, segment shortening, and stroke volume and stroke work, were similar during the initial baseline and lidocaine baseline (Table 2) suggests that neither stunning nor preconditioning were a problem in our preparation.

These experiments were done in open-chest anesthetized pigs. This preparation may have led to changes in coronary flow, and the responses to ischemia that could be different from what would have been observed in conscious animals.

In conclusion, we found that the Na\(^{+}\)-channel blocker lidocaine increased the magnitude of the shift of the diastolic pressure-volume curve that accompanies demand ischemia. This result is evidence against the hypothesis that this upward shift is due to an increase in the background level of Ca\(^{2+}\) in the myocardium. It also points to the need for clinical studies to assess the effects of lidocaine on diastolic function in patients with ischemic heart disease. The fact that lidocaine adversely affected the response of the heart to demand ischemia during diastole at a dose small enough to avoid adverse effects on systolic function is further evidence that diastolic dysfunction appears before systolic dysfunction.

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**REFERENCES**


