Electrophysiological Effects of Left Ventricular Hypertrophy

Effect of Calcium and Potassium Channel Blockade

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Background. To define the arrhythmogenic effects of left ventricular hypertrophy (LVH) in the intact heart, we carried out a detailed electrophysiological assessment in our previously validated feline aortic-banding model and then tested the effects of agents that blocked either the slow inward calcium or voltage-dependent potassium channel.

Methods and Results. We measured intraventricular and interventricular conduction times, excitability thresholds, ventricular effective refractory periods, and monophasic action potential duration at several sites in cats with LVH as well as in concurrent control (sham-operated) cats. In addition, we assessed vulnerability to ventricular arrhythmia using direct measurement of ventricular fibrillation (VF) thresholds and by standard techniques of programmed stimulation. Despite finding no difference between LVH and sham-operated cats in mean values for several electrophysiological parameters, the former group was significantly more vulnerable to VF, with more spontaneous VF and lower VF thresholds. Compared with the sham controls, LVH cats also had a greater dispersion of effective refractory period (35±11 versus 12±4 msec, p<0.01) and monophasic action potential duration at 90% repolarization (69±25 versus 39±7 msec, p<0.02). Verapamil had no significant effect on these electrophysiological parameters, nor did it affect VF threshold. However, risotilide, an inhibitor of the voltage-dependent potassium channel, narrowed dispersion of the effective refractory period and monophasic action potential duration concomitant with a marked reduction in ventricular vulnerability.

Conclusions. LVH has a pronounced effect on dispersion of refractoriness and repolarization and renders the ventricle more vulnerable to fibrillation. Blockade of the voltage-dependent potassium channel, but not the slow inward calcium channel, narrows the dispersion of recovery of excitability and protects against VF. (Circulation 1991;83:2067–2075)

The development of treatment strategies for cardiac arrhythmia that may develop in specific clinical situations requires a detailed understanding of mechanisms by which these arrhythmias are generated. Such research, in turn, depends on the availability of validated animal models, since in-depth studies require the kind of control and intervention that is not possible in the clinical setting. Heretofore, most intensive studies of cardiac arrhythmia have used ischemia/infarction models in which abnormalities of conduction give rise to malignant ventricular arrhythmia. However, it is clear that a sizable percentage of arrhythmias seen clinically are not related to coronary artery disease per se. An example is hypertrophic heart disease, associated with malignant ventricular arrhythmia and sudden cardiac death. Largely because a valid whole-animal model has not been available, the mechanism of arrhythmia generation in this syndrome remains poorly understood. Proposed in previous studies by us and others is the hypothesis that hypertrophy causes electrophysiological abnormalities quite distinct from those seen in ischemic heart disease. This report will expand on our previous experience by presenting a more in-depth analysis of the results of our in vivo experience, including the use of pharmacological “probes” that help in our understanding of the role
of cation flux in the genesis of arrhythmias associated with left ventricular hypertrophy (LVH).

Methods

General Methods

One hundred semiconditioned cats of either sex were used for the study. All studies were carried out in conformance with guidelines established by the American Heart Association regarding research animal use and according to a protocol reviewed and approved by the Animal Care and Use Committee of the Medical College of Pennsylvania. The cats were anesthetized with ketamine (10 mg/kg i.m., followed by 2.5 mg/kg i.v.), intubated using a cuffed endotracheal tube, and ventilated with nitrous oxide and oxygen via a respirator (Harvard Apparatus, South Natick, Mass.), the rate and volume of which were adjusted to maintain PO₂, PCO₂, and pH within physiological range. A warming blanket was used to maintain body temperature. Under sterile conditions, a small right anterior thoracotomy was performed one interspace superior to the cardiac apical impulse. The pericardium was opened, and the plane between the aorta and pulmonary artery was dissected. In 59 cats, a band, consisting of polyethylene tubing with 24-gauge copper wire and 0-0 silk suture through its lumen, preformed into a circle with an internal diameter of 3.2–3.5 mm was placed around the ascending aorta and sutured in place. In the other 41 cats, banding was not carried out. The chest was closed, and the animals were allowed to recover.

Approximately 1 month after surgery, we began biweekly echocardiography/Doppler ultrasound studies. The cats, after light sedation, underwent two-dimensional, M-mode, and Doppler studies performed with an Irex Meridian and a 5-MHz phased-array transducer (Johnson and Johnson, Ramsey, N.J.). Short-axis images were obtained in all cases. Diastolic measurements of the thickness of the left ventricular posterior wall were made from a derived M-mode image at a level between the mitral valve and papillary muscle using the leading-edge method. A 2.0-MHz continuous-wave imaging transducer was used to obtain Doppler flow signals in the aorta. During surgical exposure, the transducer was placed 1–2 cm above the band and angulated into the left ventricular cavity. The audible signal was optimized to obtain the highest velocities, and the subsequent spectral display was frozen. On-line measurements of peak velocity (V) were obtained and then converted to peak pressure gradients using the modified Bernoulli equation (4V²). These flow velocity spectra were then recorded using a strip-chart recorder for later reference.

A decision was made to harvest the hearts when left ventricular wall thickness had increased at least 30% over the values obtained at the initial postsurgery study. At that point, the cats were anesthetized with 50–70 mg/kg α-chloralose delivered intraperitoneally. The femoral artery and vein were cannulated with polyethylene catheters to measure blood pressure and administer drugs. A thoracotomy was performed, and the pericardium was opened. Paired transmural plunge electrodes were positioned on the anterior left ventricle, the posterolateral wall, the left ventricular apex, and the anterior surface of the right ventricle. To preserve uniformity of sampling, the sites selected were based on an estimate of proximity to major coronary artery segments. Quadrupolar pacing catheters were passed from the right and left atrial appendages to the right and left ventricular apexes. After electrical testing, the cats were killed, and the hearts were removed and placed in chilled saline. The left ventricle was isolated, and maximum wall thickness was measured with calipers. The left ventricle was weighed, and mass was expressed as a ratio of the total heart weight.

Electrical Testing

Testing was carried out using a modified Bloom stimulator (Bloom Limited, Reading, Pa.) capable of delivering constant-current rectangular impulses of from 0.1 to 100 mA with pulse widths of 2–5 msec. Electrograms were amplified and recorded on a VR 12 Physiologic Recorder (Electronics-for-Medicine, Kingwood, Tex.). Conduction times were measured within and between chambers defined as the time elapsed between earliest and latest activation at any of the recording sites. The onset of ventricular activation at any site was defined as the point at which the initial rapid deflection of the electrogram crossed the baseline. Electrograms were recorded at a paper speed of 150 mm/sec and a gain setting of 1.0 mV/cm. The sensitivity of the recording was changed by a factor of 0.5 for those recordings of varying amplitude, including action potential recordings. All results were measured at least twice and reexamined if widely disparate.

Excitability threshold was measured at all sites and was taken as the minimum current that caused consistent ventricular capture using a 2-msec stimulus introduced in late diastole. The intensity of the stimulus was increased in 0.1-mA increments until ventricular capture. Sequences that caused consistent ventricular capture were repeated to ensure reliability of the result. Ventricular effective refractory periods were obtained using twice-threshold extrastimuli delivered in 10-msec decrements during ventricular pacing at the longest cycle length that consistently captured the ventricle. Mean paced cycle lengths varied among groups by no more than 30 msec. The effective refractory period was defined as the longest S,S₂ that failed to capture the ventricle. Each stimulus that produced no capture was reintroduced to guarantee reproducibility.

Monophasic action potentials were recorded on the epicardial surface, directly contiguous to the site of the plunge electrode placement, using a hand-held Franz contact electrode (model 501, EP Technologies Inc., Mountainview, Calif.). Monophasic action potential durations (MAPDs) were measured at a
point where the deflection had reached 90% (MAPD₀) and 50% (MAPD₅₀) of complete repolarization. Values reported for all electrophysiological parameters represent a mean for all sites tested in each chamber. Dispersion of all parameters was defined as the maximum difference among all sites tested either within or between the right and left ventricles.

Right and left ventricular fibrillation thresholds (VFTs) were measured with endocardial pacing catheters using a formerly described and validated single-stimulus technique.³ A 4-mA extrastimulus with a 5-msec pulse width was introduced in midectrical diastole during ventricular pacing. The vulnerable period was scanned in 10-msec decrements until refractoriness was reached. The current was then increased in 2-mA increments, and scanning through the vulnerable period was continued until ventricular fibrillation (VF) was induced. Defibrillation was carried out within 15 seconds of the onset of VF using a 10–20 J direct current shock applied directly to the heart. After a hiatus of 15 minutes, testing was repeated to ensure reproducibility. Testing continued until VFTs varied by no more than 6 mA; the results were then averaged.

Inducibility of ventricular arrhythmia was also assessed using 2-msec, twice-threshold extrastimuli delivered via the right and left ventricular endocardial pacing catheters at the longest drive cycle that consistently captured the ventricle (250–350 msec). The method of extrastimulation used was the same as that carried out in previous studies.⁴ An initial extrastimulus (S₁) was set at twice diastolic threshold, 250 msec after the pacing artifact, and introduced progressively earlier until refractoriness was reached. If a sustained arrhythmia was not provoked, a second extrastimulus (S₂) was introduced decrementally starting 250 msec after S₂. A third extrastimulus (S₃) was used if prior stimulation did not provoke a sustained ventricular arrhythmia. The end point of testing was the induction of a sustained ventricular arrhythmia (lasting >30 seconds or requiring an intervention for termination). Sustained arrhythmias were terminated using an internal direct current shock (maximum, 10 J). Sequences that induced a sustained arrhythmia were repeated after a 15-minute respite to ensure reproducibility and were reported as positive only if seen in two of three trials.

**Experimental Design**

Ninety-two (52 banded and 40 sham-operated) surviving cats were studied in a drug-free state. After the control study, 14 (seven banded and seven sham-operated) cats received verapamil in a dose of 0.30 mg/kg i.v. followed by an infusion of 10 μg/kg/min, and testing was repeated. Fourteen (seven banded and seven sham-operated) other cats were treated with risotilide (5 mg/kg i.v.) before testing was repeated. After drug administration, the study was terminated, and the cats were killed as described previously.

### Table 1. Hypertrophy Indexes in Sham-Operated and Banded Cats

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated (n=26)</th>
<th>Banded (n=48)</th>
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<tbody>
<tr>
<td>LV wall thickness (cm)</td>
<td>0.43±0.05</td>
<td>0.67±0.08*</td>
</tr>
<tr>
<td>LV weight (g)</td>
<td>8.1±2.4</td>
<td>10.2±1.6†</td>
</tr>
<tr>
<td>LV wt/total heart wt (%)</td>
<td>60.1±10.1</td>
<td>69.3±5.8</td>
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</tbody>
</table>

Values are mean±SD. LV, left ventricular.

*p<0.001 and †p<0.05 compared with value for sham-operated cats.

**Statistical Analysis**

Results expressed in text, tables, and figures represent mean±SD. Student’s t test was used for simple two-way comparisons of data. However, multiple comparisons required analysis of variance. Results were considered significant at *p<0.05.

**Results**

A total of 92 cats were available for study. Seven of the banded cats died in the interim between banding and study, including six that died suddenly in their cages or developed VF during catheter insertion and could not be resuscitated. All of these cats had a nonsignificantly greater posterior wall thickness (0.77±0.10 versus 0.67±0.08 cm, p=NS) and weight (11.3±1.4 versus 10.2±1.6 g, p=NS) compared with cats that survived.

Time from banding to study was 150 days (105–180 days). Indexes of hypertrophy are presented in Table 1. As expected, cats that underwent banding had significantly thicker and heavier left ventricles compared with the sham-operated controls. Banded cats all had a pressure gradient from the left ventricle to the aorta above the band placement (29.8±5.7 mm Hg).

Table 2 presents the results of electrophysiological testing for the entire cohort. There were no significant differences between sham-operated and banded cats except for the excitability thresholds in the left ventricle, which were significantly higher in the banded group. Verapamil had a negligible effect on these raw measurements either in the banded or sham-operated cats. However, risotilide consistently prolonged refractoriness and repolarization in both groups. Its effect on these parameters in the left ventricle of sham-operated controls was significantly greater than that in the left ventricle of banded cats. Interestingly, this differential effect was not seen in the nonhypertrophied right ventricle. That verapamil had been administered in physiological doses is evident from the results in Table 3. Verapamil, but not risotilide, markedly prolonged atrioventricular conduction times and caused Wenckebach block in two of the banded cats.

In Figures 1 and 2 are portrayed the values for dispersion of refractoriness for untreated and treated cats, respectively. Untreated banded cats manifested a marked dispersion of the effective refractory period in the left ventricle and between the left and right...
ventricle, but not within the right ventricle, where the values were similar to those seen in the sham-operated group. This dispersion was preserved even after the results were normalized for differences in activation. In the cats treated with verapamil, dispersion was not significantly altered (Figure 2). However, treatment with risotilide resulted in a marked diminution of dispersion of refactoriness both in the left ventricle and between right and left ventricles.

Dispersion of action potential duration is illustrated in Figures 3 and 4. Once again, untreated cats had a marked difference in MAPD$_{90}$ and MAPD$_{90}$ between left and right ventricles, within the left ventricle, but not within the right ventricle. As with dispersion of refractoriness, the dispersion of action potential duration persisted when the values were normalized for the small differences in ventricular activation. In Figure 4, it is evident that risotilide, by prolonging MAPD at several sites, abolished regional differences in MAPD in the left ventricle, causing a reduction in dispersion to values approximating those seen in the right ventricle.

Finally, we examined the dispersion of excitability thresholds in and between the two ventricles. Figure 5 demonstrates a significantly greater dispersion of excitability threshold in the banded cats that was most evident in the left ventricle. Risotilide, but not verapamil, partially returned this dispersion toward control values in the banded cats, as seen in Figure 6.

Direct measurements of VFTs are illustrated in Figures 7 and 8. Both right and left VFTs were lower in the banded compared with the sham-operated cats. Verapamil had no significant effect on VFTs in either group. Note that the VFTs were as low in the right as in the left ventricle, even though the electrophysiological abnormalities induced by LVH were seen predominantly in the left ventricle. Risotilide raised VF thresholds in the sham-operated cats and had a pronounced effect in the banded group. The VFTs obtained after risotilide were akin to those seen before drugs in the sham-operated group.

The results of programmed stimulation are presented in Table 4. In all cases in which a sustained arrhythmia was induced, two or three extrastimuli were required, and the arrhythmia induced was always VF. Monomorphic ventricular tachycardia was never seen in these cats. Only one of 26 sham-operated cats was induced to VF compared with 22 of 42 banded cats ($p<0.05$). Of the seven banded cats treated with verapamil, five were induced before drug administration, and four of these remained inducible after drug administration. Conversely, risotilide rendered arrhythmia noninducible in all six of the banded cats that had been induced at baseline.

### Table 2. Electrophysiological Measurements in Sham-Operated and Banded Cats

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated</th>
<th></th>
<th></th>
<th>Banded</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Untreated $(n=26)$</td>
<td>Verapamil $(n=7)$</td>
<td>Risotilide $(n=7)$</td>
<td>Untreated $(n=38)$</td>
<td>Verapamil $(n=7)$</td>
<td>Risotilide $(n=7)$</td>
</tr>
<tr>
<td>SCL (msec)</td>
<td>290±19</td>
<td>332±99</td>
<td>338±22</td>
<td>294±45</td>
<td>299±42</td>
<td>316±24</td>
</tr>
<tr>
<td>RIVCT (msec)</td>
<td>37.4±4.4</td>
<td>35.8±1.8</td>
<td>34.6±1.9</td>
<td>34.9±9.3</td>
<td>35.2±2.3</td>
<td>33.9±2.6</td>
</tr>
<tr>
<td>LIVCT (msec)</td>
<td>36.9±4.2</td>
<td>33.6±3.4</td>
<td>32.7±2.0</td>
<td>33.1±9.7</td>
<td>34.1±2.1</td>
<td>32.0±2.6</td>
</tr>
<tr>
<td>R-L IVCT (msec)</td>
<td>39.9±6.1</td>
<td>40.0±3.1</td>
<td>36.6±3.5</td>
<td>37.6±6.3</td>
<td>37.2±2.9</td>
<td>36.4±2.3</td>
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<tr>
<td>ET LV (mA)</td>
<td>0.47±0.15</td>
<td>0.64±0.05*</td>
<td>0.63±0.07*</td>
<td>0.60±0.21†</td>
<td>0.81±0.18*</td>
<td>0.81±0.19*</td>
</tr>
<tr>
<td>ET RV (mA)</td>
<td>0.42±0.18</td>
<td>0.48±0.11</td>
<td>0.49±0.15</td>
<td>0.44±0.17</td>
<td>0.47±0.12</td>
<td>0.52±0.18</td>
</tr>
<tr>
<td>ERP LV (msec)</td>
<td>147±15</td>
<td>138±7.6</td>
<td>183±15*</td>
<td>147±22</td>
<td>141±16.3</td>
<td>171±17*</td>
</tr>
<tr>
<td>ERP RV (msec)</td>
<td>149±19</td>
<td>143±5.0</td>
<td>186±17*</td>
<td>146±19</td>
<td>147±16.1</td>
<td>180±17*</td>
</tr>
<tr>
<td>MAPD$_{90}$ RV (msec)</td>
<td>175±18</td>
<td>177±18.3</td>
<td>215±21*</td>
<td>177±21</td>
<td>180±16.1</td>
<td>202±21*</td>
</tr>
<tr>
<td>MAPD$_{90}$ LV (msec)</td>
<td>173±23</td>
<td>180±16.1</td>
<td>220±21*</td>
<td>190±36</td>
<td>186±19.2</td>
<td>203±18*†</td>
</tr>
<tr>
<td>MAPD$_{90}$ RV (msec)</td>
<td>148±15</td>
<td>147±17.3</td>
<td>174±14*</td>
<td>151±26</td>
<td>148±14.2</td>
<td>162±14*</td>
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<tr>
<td>MAPD$_{90}$ LV (msec)</td>
<td>145±19</td>
<td>150±15.1</td>
<td>175±19*</td>
<td>159±39</td>
<td>159±20.02</td>
<td>156±15†</td>
</tr>
</tbody>
</table>

Values are mean±SD. SCL, sinus cycle length; R, right; L, left; IVCT, interventricular conduction time; ET, excitability threshold; LV, left ventricle; RV, right ventricle; ERP, effective refractory period; MAPD$_{90}$ and MAPD$_{90}$, monophasic action potential duration at 90% and 50% repolarization, respectively.

* $p<0.05$ compared with corresponding value for untreated cats; † $p<0.05$ compared with corresponding value for sham-operated cats.

### Table 3. Atrioventricular Conduction in Sham-Operated and Banded Cats

<table>
<thead>
<tr>
<th></th>
<th>Sham-operated</th>
<th></th>
<th></th>
<th>Banded</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Predrug conduction (sec)</td>
<td>Postdrug conduction (sec)</td>
<td>Predrug conduction (sec)</td>
<td>Postdrug conduction (sec)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.069±0.006</td>
<td>0.087±0.006*</td>
<td>0.060±0.005</td>
<td>0.079±0.004†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risotilide</td>
<td>0.064±0.006</td>
<td>0.066±0.008</td>
<td>0.063±0.006</td>
<td>0.065±0.005</td>
<td></td>
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</tr>
</tbody>
</table>

Values are mean±SD.

* $p<0.001$ compared with corresponding predrug value.
† Two cats developed spontaneous Wenckebach block.
which there operated cats banded with these numbers are not large enough to perform valid statistical comparisons.

Discussion

Abundant information is now available to prove that hypertrophy of ventricular myocardium is highly arrhythmogenic. Most of these data come from clinical trials in which patients with LVH have been shown to have high densities of ventricular arrhythmia, many times complex. Messerli et al. and McLenachan et al. both proved that patients with hypertension and LVH had more frequent and more complex ventricular arrhythmia than those with hypertension that had not progressed to hypertrophy. That this arrhythmia has clinical significance has been substantiated by data from Framingham, in which there has been shown to be an excess incidence in sudden death among the cohort whose electrocardiograms showed evidence of LVH. Patients with aortic stenosis who develop LVH have a remarkably high incidence of sudden death, which does not diminish if valve replacement does not cause a reversal of the process. Malignant arrhythmias and sudden death are common features of rarer forms of ventricular hypertrophy such as hypertrophic obstructive cardiomyopathy, in which hypertrophy is accompanied by a marked disorganization of myocardial architecture. Nevertheless, a causal relation between the high density of complex ventricular arrhythmias seen in patients with LVH and sudden cardiac death has not been established.

Despite these clinical data, our knowledge of the mechanisms of these arrhythmias is quite primitive.
Cameron et al\textsuperscript{7} conducted one of the earliest studies in this area. They subjected cats to aortic banding, which caused a 15–20% reduction in luminal diameter. After 1–8 months, the hearts were harvested. A 60% increase in left ventricular mass that was associated with multiple patchy fibrotic regions interspersed with normal myocardium was noted. Using microelectrode techniques, Cameron et al showed that cells with normal and abnormal action potentials were contiguous. This heterogeneity in action potential characteristics, including action potential duration, was thought to provide a milieu for the genesis of malignant ventricular arrhythmia.

Because of the marked abnormalities in action potential duration, there has been growing interest in the ion channels that are operative during this phase of the cardiac cycle.\textsuperscript{15} Prolongation of the action potential, the most prominent electrophysiological abnormality in the hypertrophied cells, may be due in part to an increase in the slow inward calcium current that maintains depolarization during the plateau phase.\textsuperscript{16} Alternatively, some investigators have suggested that plateau-phase abnormalities may be caused by attenuation of one or several of the outward potassium currents, such as the ATP-sensitive channel, the delayed rectifier current, or even the transient outward current.\textsuperscript{17–19} All of these possibilities have been explored in isolated tissue.

Although intriguing, these hypotheses have not been tested in an intact animal model and certainly not in humans. The cat aortic-banding model has some advantages, the most important of which is that the clinically correct ventricle is used.\textsuperscript{5} The disadvantage is that the band is placed above the coronary circulation, and so any changes that are induced in coronary dynamics may not replicate what happens clinically.\textsuperscript{20}
We6 previously published our results in this model. An increase in left ventricular mass was associated with an increase in vulnerability to VF without any measurable change in either pacing thresholds or refractoriness. Threshold for VF in this model, as well as in others, appears to be reliably measured in either ventricle and reflects the relative propensity to develop the arrhythmia spontaneously.6,9 The earlier study was not designed to determine the effect of interventions, nor were a sufficient number of animals used to draw firm conclusions.

The present study has several relevant findings. First, LVH can be provoked with regularity using an aortic band. Echocardiography/Doppler ultrasound can be used to monitor the process, providing for optimal time of harvesting. Animals with LVH are susceptible to VF, and this propensity can be measured as a lowering of the threshold current needed to provoke VF from either ventricle and in the tendency to provoke this arrhythmia using sequential extrastimuli.

Vulnerability to VF was not reflected in any of the parameters that are routinely measured in the clinical laboratory. There was little difference between LVH and sham-operated controls with regard to absolute values for conduction times, refractory periods, or MAPDs. Excitability thresholds were statistically, but probably not meaningfully, higher in the cats with LVH, perhaps reflecting the need for higher currents to stimulate fibrotic tissue.

FIGURE 6. Bar graph showing dispersion of excitability thresholds in control and treated cats that were either banded or sham-operated. Values are presented for dispersion among left ventricular sites (LV-LV) and between left and right ventricular sites (LV-RV). Dispersion of excitability thresholds was generally greater in the banded group compared with the sham-operated control group and was statistically lower in the risotilide-treated group compared with either the control group or the verapamil-treated group. *p<0.05 compared with the control group.

FIGURE 7. Bar graph showing ventricular fibrillation thresholds (VFTs) measured in milliamperes in untreated banded and sham-operated cats within the left ventricle (LV) and right ventricle (RV). The VFT was significantly lower in the banded group when tested in either chamber. *p<0.05 compared with the banded group.

FIGURE 8. Bar graph showing ventricular fibrillation thresholds measured in milliamperes in control and treated cats within the left ventricle (LV) and right ventricle (RV). Thresholds were lower in the banded group and were restored to values comparable with the sham-operated group with administration of risotilide but not with verapamil. *p<0.05 compared with the control group.
Cats with LVH did have a striking difference from site to site in ventricular effective refractory periods and action potential duration. These findings are in line with the hypothesis that vulnerability is increased in a milieu in which there are marked differences in electrical properties in contiguous cells. The dispersion of excitability thresholds (and perhaps the observation that excitability thresholds in the banded group were significantly different from those in the sham-operated group) may be explained by the inhomogeneity of recovery of excitability manifest as dispersion of refractoriness and repolarization times.

The use of direct action potential recordings in vivo represents a significant advance in our ability to discern electrophysiological changes in the intact heart. This technique has been used to measure changes in repolarization time under diverse physiological conditions and during pharmacological interventions. We found that LVH itself caused a prolongation of left ventricular (but not right ventricular) MAPD measured when the action potential had recovered 90% or 50% to its baseline voltage. The standard deviations for these values were so wide that the differences did not reach statistical significance. However, the dispersion of action potential duration was significantly greater in the hypertrophied left ventricle than in the right ventricle of the banded group or either ventricle of the sham-operated group.

The results of earlier investigations strongly suggest that calcium flux is an important principle in the development of the arrhythmias that accompany LVH and that blockade of the slow current calcium channel might protect against these arrhythmias. Although calcium channel blockade appears to prolong action potential duration in vitro, we saw no significant change in the intact animal. Nor did we observe a change in refractoriness or in dispersion of refractoriness or MAPD. It is conceivable that, if verapamil has an antiarrhythmic effect, its protection may be afforded by modifying the trigger for these arrhythmias rather than the substrate.

In contrast to the results with verapamil, we noted a marked electrophysiological effect of potassium channel blockade, specifically inhibition of the voltage-dependent potassium channel with risotilide. As expected, and previously reported, risotilide prolonged refractoriness and repolarization time in both the hypertrophied and normal ventricle. Interestingly, the absolute amount of prolongation was less in the hypertrophied than in the nonhypertrophied ventricle, which may argue that hypertrophy changes either the density or kinetics of this particular potassium channel. Because of its very potent effects on the effective refractory period and MAPD in all tissue, risotilide restored homogeneity manifest as a significant reduction in dispersion of these properties. In addition, the dispersion of excitability threshold, which we attributed to a varying ability of partially recovered cells to reexcite, was restored. These findings coincided with a marked reduction in vulnerability with a restoration of VFTs toward control values and inability to induce VF using programmed stimulation.

The mechanism by which modulation of the voltage-dependent potassium channel alters ventricular electrical properties in animals with LVH is not clear. Dispersion of refractoriness has been shown to be an important principle in the genesis of VF in the ischemic setting. Drugs, such as bretylium or amiodarone, that restore homogeneity, protect against ventricular arrhythmias in these models. It does appear that drugs that primarily exert their electrophysiological effect on the plateau phase of the action potential may have particular usefulness. These issues do underscore the point that hypertrophy causes abnormalities in refractoriness and repolarization unlike infarction, which predominantly affects conduction. Thus, therapy for arrhythmias in these settings may be quite different.

As has been pointed out, modulation of the potassium channel is a complex issue. There appear to be a number of potassium channels in the heart and peripheral vasculature. It is not clear whether drugs such as risotilide are specific for any one of these currents in any particular tissue, nor is it clear which current may be preeminent in any disease state. It may well be that prolongation of refractoriness is an overly simple concept in understanding the way in which an antiarrhythmic drug that has an effect on a potassium channel protects against ventricular arrhythmia.

Our study has limitations that should be emphasized. The number of animals included in the drug treatment groups was relatively small compared with the total cohort. However, the results were strikingly consistent throughout all of the experimental groups. The model used is a whole-animal preparation, which precludes observation at the cellular level. The technique used to define electrophysiological changes was recording of MAPDs using a contact electrode. Changes in action potential duration defined by this technique have been shown to correlate with changes at the cellular level. We would also emphasize that we made no attempt to quantitate spontaneous arrhythmias, and so any firm conclusions regarding relevance to the clinical situation in which ectopy is routinely observed is unwarranted.

### Table 4. Inducibility of Sustained Arrhythmia by Programmed Stimulation in Sham-Operated and Banded Cats

<table>
<thead>
<tr>
<th>Group</th>
<th>Before Drug</th>
<th>After Drug</th>
<th>Before Drug</th>
<th>After Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0/12</td>
<td>. .</td>
<td>11/28</td>
<td>. .</td>
</tr>
<tr>
<td>Verapamil</td>
<td>0/7</td>
<td>0/7</td>
<td>5/7</td>
<td>4/7</td>
</tr>
<tr>
<td>Risotilide</td>
<td>1/7</td>
<td>0/7</td>
<td>6/7</td>
<td>0/7</td>
</tr>
<tr>
<td>Total</td>
<td>1/26</td>
<td>0/14</td>
<td>22/42*</td>
<td>4/14</td>
</tr>
</tbody>
</table>

Values represent number of cats induced number of cats stimulated.

*p < 0.01 compared with corresponding value for sham-operated cats.
It should be understood that our results do not clearly demonstrate a causal relation between electrophysiological changes and VF. However, the fact that drugs that caused a reversal of those abnormalities also protected against VF is somewhat compelling. We would also caution against extrapolating our results to other drugs in the same class, or certainly to any clinical setting. The model used for our experiments produced LVH but, as stated previously,20 did not account for changes that may occur in the coronary bed, including coronary flow reserve, in animals or humans that develop LVH in the settings of aortic stenosis or hypertension.

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