Hemodynamic and Reflex Sympathetic Control of Transmural Activation and Rate of Ventricular Tachycardia in Ischemic and Hypertrophic Ventricular Myocardium of the Dog

James R. Hopson, MD, and James B. Martins, MD

**Background.** A previous study found that the electrophysiological response to ischemia is altered in hypertrophic myocardium, resulting in prolonged transmural activation time (TAT) associated with induction of sustained monomorphic ventricular tachycardia. This study investigated the role of hemodynamics in modulating TAT and the cycle length of induced ventricular tachycardia (VT) in dogs with left ventricular hypertrophy (LVH).

**Methods and Results.** Anesthetized open-chest dogs underwent 3 hours of uninterrupted circumflex coronary occlusion. During atrial drive, TAT was recorded between endocardial and epicardial bipolar pairs on the same multipolar plunge needle placed in nonischemic and ischemic zones, documented by triphenyltetrazolium chloride staining. TAT and VT induced by up to three extrastimuli were studied during hypertension (control), during normotension produced most frequently by nitroprusside infusion (3–6 μg/kg/min), and during further hypertension most frequently produced by phenylephrine infusion (1–5 μg/kg/min). Twenty-five dogs with chronic hypertension and LVH (group 1) produced by a single-kidney renal clamp mechanism and 15 control dogs were studied. In the latter, neither intervention altered TAT, and no VT was inducible. In group 1, however, nitroprusside reversibly prolonged TAT within the ischemic zone (mean±SEM, 31±3 to 34±3 msec, p<0.005) and cycle length of induced VT (204±19 to 240±17 msec, p<0.001). Phenylephrine reversibly shortened both TAT in the ischemic zone (33±2 to 28±2 msec, p<0.05) and cycle length of VT (219±17 to 165±11 msec, p<0.025). Cycle length of VT and TAT were dissociated from blood pressure elevation in two dogs with LVH; when blood pressure was elevated by sympathetic nerve stimulation, cycle length of VT and TAT were prolonged. In 11 dogs with LVH (group 2), prolongation of TAT with nitroprusside infusion was prevented by intravenous metoprolol (1.0 mg/kg). Of 12 dogs with LVH and inducible VT (group 3), seven still had VT inducible after metoprolol, but the cycle length of VT was still prolonged with nitroprusside infusion.

**Conclusions.** These results suggest that 1) TAT in acutely ischemic LVH was uniquely responsive to hemodynamic influences, an effect prevented by β-blockade with metoprolol, and 2) the cycle length of VT was also uniquely regulated by hemodynamic influences but not blocked by metoprolol. (*Circulation* 1992;86:618–627)

**KEY WORDS** • arrhythmias • hypertension • coronary occlusion

Patients with left ventricular hypertrophy (LVH) caused by chronic hypertension have an increased risk of sudden death after myocardial infarction compared with normotensive patients without hypertrophy.1–3 Dogs with one-kidney, one-clip re-
reflex changes in sympathetic tone produced by alterations in aortic pressure might mediate this electrophysiological observation.

In this article, we report experiments designed to examine the role of hemodynamics in modulating the rate and duration of VT, as well as associated electrophysiological changes in this model. We investigated the possibility that autonomic influences or deterioration of collateral blood flow provided the mechanism of hemodynamic modulation of the electrophysiological changes.

**Methods**

Mongrel dogs (20–30 kg) were made hypertensive by the following procedure. Under sterile conditions, the animals were anesthetized with sodium pentobarbital (25 mg/kg i.v.) and mechanically ventilated. Through a midline abdominal incision, both kidneys were exposed. A nephrectomy was performed on one side, and a clamp was placed on the renal artery of the contralateral kidney and tightened to produce a thrill. The wound was then closed.

Eight weeks later, these animals and normotensive control dogs (20–30 kg) were anesthetized with morphine sulfate (2.3 mg/kg i.m.) and α-chloralose (80 mg/kg i.v.); α-chloralose was then administered by constant intravenous infusion (9 mg/hr) for the remainder of the study.7 The dogs were ventilated via auffed endotracheal tube on a volume-cycled respirator with air enriched with oxygen. Minute ventilation was adjusted, and sodium bicarbonate (20 mEq/hr i.v.) was given to maintain arterial pH and P\textsubscript{CO\textsubscript{2}} within the normal range. The right femoral artery was cannulated with a 40-cm-long, 1.77-mm-i.d., fluid-filled polyethylene catheter advanced to the aortic arch and connected to a Statham P23dB transducer to monitor pressure. Mean aortic pressure (MAP) was determined by electrical filtering.

The sternum was split, and the pericardium was incised and sutured to the sternum to support the heart. A plastic sheet was placed over the open chest to prevent heat and moisture loss. Core temperature was measured by thermistor probe placed in the pulmonary artery; temperature was maintained by a heating pad and heat lamp.8 The left circumflex coronary artery was exposed in the atioventricular (A-V) groove just distal to the first marginal branch, and a 2-0 silk ligature was placed around the vessel. The suture was passed through a 10-cm portion of polyethylene tubing to form a snare, allowing occlusion of the vessel without removal of the plastic sheet. Visible collateral vessels to the left circumflex perfusion field were isolated in a similar fashion. A pulmonary vein was cannulated with a saline-filled polyethylene catheter (i.d., 1.77 mm), which was then advanced to the left atrium for measurement of mean atrial pressure and injection of microspheres. Left ventricular end diastolic cavity dimension was determined by ECG-gated M-mode and/or two-dimensional echocardiography.9

**Electrophysiological Methods**

The region of the sinus node was crushed, and a bipolar electrode was attached to the right atrial appendage for pacing and/or recording purposes. VT was defined as a rapid, wide-QRS rhythm with A-V dissociation and was considered sustained if it lasted 30 seconds or required prior termination because of hemodynamic collapse. Ventricular fibrillation was defined as rapid, disorganized ventricular activity without measurable pulse pressure.

Surface ECGs were recorded by use of standard surface leads I, aVF, and V\textsubscript{16}.

**Ventricular bipolar electrograms.** These were recorded from four to six 16-pole (1-mm interelectrode distance) plunge needles inserted perpendicularly into the left ventricular wall remote from the papillary muscles in the perfusion fields of the left anterior descending and left circumflex coronary arteries. Endocardial and epicardial bipolar electrograms were recorded from the same plunge needle using a multichannel switching system.8 The signals were amplified and filtered at 40–500 Hz and intermittently recorded during atrial pacing on an oscillographic recorder at a paper speed of 400–500 mm/sec as well as on FM tape. Endocardial bipolar electrograms were defined as those electrograms with the earliest electrical activation of all the pairs on one needle, which frequently contained Purkinje spikes.7,8 Epicardial electrograms were taken from the outermost bipolar pair of electrodes and were the latest activated on that needle during atrial pacing. Transmural activation was measured from the earliest rapid deflection of the endocardial bipolar electrogram (usually a Purkinje spike) to that on the epicardial electrogram (Figure 1). Analysis was performed only on electrograms that demonstrated the same configuration throughout all interventions of a protocol (Figure 1).

**Extra刺激ulus testing.** The effective refractory period (ERP) was measured at each epicardial and endocardial site by the following method.7 Stimuli were delivered to atria and ventricles separately and simultaneously by a programmable stimulator with separate constant-current outputs. Cathodal ventricular stimuli were delivered to one of the electrodes 1 mm from the pair of electrodes recording bipolar electrograms. Stimuli were 2 msec in duration and four times diastolic threshold. The anode was a flat, stainless steel plate in the abdominal skin. A train of seven basic stimuli (S\textsubscript{1}S\textsubscript{2}S\textsubscript{3}) was followed by a test stimulus (S\textsubscript{4}) to each site. A train delay of 750 msec was used. Initially, the S\textsubscript{1}S\textsubscript{2} interval was adequate to result in a propagated response. Thereafter, the S\textsubscript{1}S\textsubscript{2} was shortened by 2-msec intervals until S\textsubscript{2} failed to capture the ventricle. The ERP was defined as the longest S\textsubscript{1}S\textsubscript{2} that failed to capture the ventricle.7

![Figure 1. Surface leads II and V16 and bipolar electrograms from the normal zone and epicardium and endocardium from within the ischemic zone (on the same 16-pole needle) during hypertension and after mean aortic pressure was lowered by nitroprusside infusion (normotension). Transmural activation time (TAT) was measured from the most rapid deflections on the endocardial and epicardial recordings (arrows). TAT prolonged from 50 msec (left) to 57 msec (right).](image-url)
Arrhythmia induction. In each dog, pacing protocols were performed as follows. After ERP was determined, the S3S1 was prolonged by 50 msec greater than the ERP, and an S1 was added to the protocol, with the initial S3S1 interval equal to S2S3. A train delay of an appropriate length was added after S1 so that the spontaneous occurrence of arrhythmias could be recorded. The intervals were then shortened until refractoriness of both occurred. If no sustained VT was induced by the above protocol, a third extrastimulus (S4) was added.

During a hemodynamic intervention, measurements of ventricular ERP were repeated. Induction of VT was first attempted at the pacing site from which VT was induced previously, first using double and triple extrastimuli if needed. Additional sites were used if induction was not successful from the initial location. All induced VTs were recorded on FM tape as well as on an oscillographic chart recorded at a paper speed of 100–500 mm/sec. The recordings consisted of at least two surface ECG leads, at least one transmural recording from the normal zone, and four or more transmural recordings from the ischemic zone.

Determinations of infarct distribution and left ventricular mass. At the end of the experiment, the heart was removed from the chest, and the left ventricle was isolated and weighed to the nearest gram. The sites of the multipolar plunge needles were marked with stainless steel pins, and the left ventricle was sectioned into 8-mm-thick rings perpendicular to the long axis. The rings were placed in a 1% phosphate-buffered solution of triphenyltetrazolium chloride (TTC) that had been heated to 37°C for 5–10 minutes. After 20 minutes in the solution, the rings were removed and placed in 10% formaldehyde. Later, these rings were placed between Plexiglas layers and traced with a fine-point felt-tipped pen. The outer and inner aspects of the ring were traced, as well as the area of dehydrogenase-depleted myocardium representing the infarcted or damaged zone, which was pale gray; the dehydrogenase-containing myocardium stained brick red. The position of each multipolar needle was also marked on the tracings to characterize recording sites from normal and subendocardially and transmurally infarcted sites.

Measurements of regional myocardial perfusion. These were made with carbonized radioactive microspheres in the diameter of 15 µm. For each flow measurement, 6 × 10⁴ microspheres were injected through the left atrial catheter, which was subsequently flushed with saline over 10 seconds. Arterial blood for a reference sample was withdrawn simultaneously from two arterial catheters (one in the aortic arch and the other in the subclavian artery) at a constant rate of 4.32 ml/min. The dog was systemically heparinized (5,000 units i.v. every 45 minutes) to ensure thorough mixing and sampling.

For analysis of perfusion, myocardial samples were obtained from the following regions: normally perfused (nonrisk) region perfused by the left anterior descending artery and stained red by TTC, border areas (immediately adjacent to the unstained area), and the infarct region (within the center of the unstained area). An average of 12–15 g of tissue was taken from normal areas, and all the ischemic and border areas were sampled. Subsequent analysis was similar to that previously published.

Protocols

All dogs underwent the following sequence of experimental interventions. After multipolar electrodes were placed and electrograms and hemodynamic parameters were recorded, the circumflex coronary artery was ligated, as were visible epicardial collaterals to the left circumflex perfusion field. If ventricular fibrillation occurred that required more than several countershocks or any pharmacological intervention to achieve a successful resuscitation, no further electrophysiological testing was performed, to exclude the possibility that ventricular damage or drugs altered the results. Repeat measurements were made at 3 hours, followed by extrastimulus testing. If VT was induced and sustained, attempts to stop it were made by rapid overdrive pacing from the site at which induction occurred. VT induction was repeated twice before interventions were performed.

In the first series of experiments, 25 dogs with LVH (group 1) and 15 control dogs were subjected to interventions designed to both raise and lower MAP, the sequence determined by random assignment. To lower MAP, we generally chose sodium nitroprusside infusion (3–6 µg/kg/min i.v.); other methods included inferior vena cava occlusion (three of LVH group 1 and four control dogs) and nitroglycerin infusion (10–50 µg/min i.v.; two of LVH group 1). Because the responses in TAT and cycle length of VT to each method of hypotension were similar, the data were pooled. To raise MAP further, phenylephrine (1–5 µg/kg/min i.v.) was infused; other methods included descending aortic occlusion (one of LVH group 1 and two controls) and methoxamine infusion (0.1–0.4 µg/kg/min i.v.; two of LVH group 1). Because the changes in activation time were similar with these hypertensive interventions, the data were pooled. In an attempt to dissociate the influence of blood pressure from that of sympathetic activation, two additional dogs were examined in LVH group 1. In these two experiments, TAT and cycle length of VT were examined initially during phenylephrine infusion and again during sympathetic nerve stimulation titrated to similar levels of aortic pressure.

Dogs had MAP both raised and lowered if hemodynamic parameters returned to baseline after the first intervention. As our purpose was to investigate the electrophysiology associated with sustained monomorphic VT, only dogs with LVH and inducible VT (25 of 36 dogs screened) were included in group 1.

In a second series of experiments, 15 dogs with hypertension and LVH (LVH group 2) underwent testing 3 hours after circumflex coronary occlusion to assess whether the transmural activation changes observed within the LVH group were a result of autonomic influences. These dogs did not undergo extrastimulus protocols to induce VT. However, they did have echocardiographic and regional blood flow measurements. In this group, two dogs underwent sequential nitroprusside infusions without autonomic intervention to demonstrate reproducibility, and two dogs received atropine (0.1 mg/kg i.v.) between sequential nitroprusside infusions to determine whether parasympathetic influences alone were responsible for changes in activation time. In the remaining 11 dogs, metoprolol (1.0 mg/kg i.v.) was given over 20 minutes before the...
Table 1. Hemodynamic and Left Ventricular Mass Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean aortic pressure (mm Hg)</th>
<th>Atrial paced cycle length (msec)</th>
<th>Left atrial pressure (mm Hg)</th>
<th>LV mass (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVH group 1</td>
<td>97±5*</td>
<td>382±6</td>
<td>10.6±1.4</td>
<td>140±7*</td>
</tr>
<tr>
<td>(n=25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH group 2</td>
<td>97±11*</td>
<td>386±5</td>
<td>11.3±2.0</td>
<td>131±6*</td>
</tr>
<tr>
<td>(n=15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH group 3</td>
<td>123±5*</td>
<td>382±17</td>
<td>12.0±0.9</td>
<td>139±7*</td>
</tr>
<tr>
<td>(n=12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>76±8</td>
<td>383±5</td>
<td>8.0±1.7</td>
<td>106±6</td>
</tr>
<tr>
<td>(n=15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LV, left ventricular; LVH, left ventricular hypertrophy. *p<0.05 vs. controls.

Table 2. Hemodynamic and Activation Changes: Control Group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypotensive intervention Before</th>
<th>Hypotensive intervention During</th>
<th>Hypertensive intervention Before</th>
<th>Hypertensive intervention During</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>80±5</td>
<td>35±3*</td>
<td>77±7</td>
<td>126±7*</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>5±1</td>
<td>2±1*</td>
<td>8±1</td>
<td>9±1</td>
</tr>
<tr>
<td>Transmural activation times (msec)</td>
<td>26±3</td>
<td>26±3</td>
<td>29±6</td>
<td>28±6</td>
</tr>
<tr>
<td>Normal zone</td>
<td>10±2</td>
<td>10±2</td>
<td>14±2</td>
<td>14±2</td>
</tr>
<tr>
<td>LV end diastolic diameter (mm)</td>
<td>29±1</td>
<td>22±1*</td>
<td>30±9</td>
<td>31±8</td>
</tr>
</tbody>
</table>

LV, left ventricular. *p<0.01 compared with before intervention.

Statistical Analysis

All data are expressed as mean±SEM. Within groups, changes in parameters during various hemodynamic interventions were compared with a Student’s t test for paired samples.13 Within groups, regression analysis was used to compare changes in transmural activation time with changes in other measured variables.13 Between groups, data were compared with a Student’s t test for unpaired samples.

Results

As expected, all LVH groups had higher MAP and left ventricular mass measurements than did the control group (Table 1). There was no difference among the LVH groups in MAP or left ventricular mass.

Control Group

The changes in hemodynamic variables, including the changes in MAP, ERP, and TAT within the control group, are shown in Table 2. No changes were seen in activation time of ischemic or nonischemic zones as MAP was either lowered or raised. No sustained monomorphic VT was inducible in any control dog.

Left Ventricular Hypertrophy Groups

Of the 25 dogs in LVH group 1, four dogs had MAP raised, 16 had MAP lowered, and five had both; nine dogs had MAP raised first and 16 had MAP lowered first. The changes in hemodynamic variables and activation times with each intervention are shown in Table 3. With reduction of MAP, TAT prolongation was observed only in the ischemic zone and returned toward control levels when MAP returned to baseline (Figure 2). This effect on TAT was seen both in infarcts that were transmural and in those that were limited to the endocardium. Conversely, raising MAP shortened TAT, again only within the ischemic zone, which also returned toward control levels when aortic pressure fell to baseline (Figure 3). There was a weak correlation (r<0.5) between the baseline value of TAT and the magnitude of the subsequent change observed during either elevation or reduction in aortic pressure.

Changes in aortic pressure were also associated with changes in the cycle length of inducible VT. In response to a reduction in MAP, the cycle length of VT was prolonged, and as MAP was artificially elevated, the cycle length of the VT shortened (Figure 4). Of the 21 dogs in group 1 subjected to a hypotensive intervention, eight had the same VT morphology before and after hypotension (Figure 4), 11 were rendered nonsustained

Table 3. Hemodynamic and Activation Time Changes: Left Ventricular Hypertrophy Group 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Hypotensive intervention (n=21)</th>
<th>Hypertensive intervention (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>112±6</td>
<td>92±3</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>11±4</td>
<td>9±4*</td>
</tr>
<tr>
<td>Transmural activation times (msec)</td>
<td>31±3</td>
<td>33±2</td>
</tr>
<tr>
<td>Normal zone</td>
<td>16±1</td>
<td>14±1</td>
</tr>
<tr>
<td>LV end diastolic diameter (mm)</td>
<td>26±2</td>
<td>26±3</td>
</tr>
</tbody>
</table>

LV, left ventricular. *p<0.05 compared with before intervention.
or noninducible, one was inducible only during nitroprusside infusion, and one had a VT morphology that was different in either surface configuration or the sequence of intracardiac electrograms. Of the nine dogs in group 1 subjected to a hypertensive intervention, five had the same VT morphology before and after hypertension (Figure 4), three were rendered noninducible, and one had a dissimilar VT morphology. Although comparisons of cycle length were made between interventions only when VT was similar in both surface

**Figure 2.** Graphs showing changes in mean aortic pressure and transmural activation time (TAT) during nitroprusside and recovery in left ventricular hypertrophy group 1. Only TAT in ischemic zone prolonged reversibly as aortic pressure fell.

**Figure 3.** Graphs showing changes in mean aortic pressure and transmural activation time (TAT) during phenylephrine and recovery in left ventricular hypertrophy group 1. Only TAT in ischemic zone shortened reversibly as aortic pressure was elevated.
morphology and the sequence of intracardiac electrograms (Figure 5), inclusion of dissimilar VTs would not have changed the results. Changes in both normal and ischemic zone ERP seen during an intervention correlated poorly ($r<0.3$) with the magnitude of change in TAT or cycle length of VT.

To examine the relative influence of reflex sympathetic and direct hemodynamic effects of raising MAP on TAT, experiments were performed on two dogs in which phenylephrine infusion was followed by sympathetic nerve stimulation. Both interventions produce similar changes in aortic pressure but would have opposite effects on cardiac sympathetic neural input. As before, phenylephrine shortened TAT and cycle length of VT. When MAP was elevated with sympathetic nerve stimulation to levels similar to those during phenylephrine, the cycle length of induced VT and TAT were prolonged (Figure 6).

The effects of autonomic blockade on TAT were investigated further in LVH group 2. Two dogs of this group were given two consecutive nitroprusside infusions without other intervention, each demonstrating that prolongation of TAT in the ischemic zone is reproducible over sequential hypotensive episodes. In another two dogs from LVH group 2, atropine was used to investigate possible parasympathetic influence. An initial nitroprusside infusion demonstrated reversible TAT prolongation, which was followed by atropine administration and repeat nitroprusside infusion. Atropine did not itself alter TAT and did not alter the prolongation of TAT during a subsequent nitroprusside infusion in either animal. The results of similar experiments performed in the remaining 11 dogs of LVH group 2, exploring the ability of $\beta$-blockade with metoprolol (1.0 mg/kg i.v.) to alter the ability of hypotension to prolong TAT, are shown in Table 4. As expected, the initial nitroprusside infusion produced reversible prolongation of TAT. The administration of metoprolol alone was found to have no effect on TAT, and there was no evidence of heart failure with metoprolol. Subsequent nitroprusside infusion, titrated to the same MAP as reached before metoprolol, had no effect (Figure 7). Moreover, although nitroprusside infusion after $\beta$-blockade resulted in a decrease in collateral

![Graph showing changes in cycle length of ventricular tachycardia with nitroprusside and phenylephrine](image)

**Figure 4.** Graphs showing changes in the cycle length of ventricular tachycardia with nitroprusside (left panel) and phenylephrine (right panel) in left ventricular hypertrophy group 1. Cycle length prolonged as mean aortic pressure was reduced and shortened as aortic pressure was elevated.

![ECG of ventricular tachycardia (VT) induced in one dog from left ventricular hypertrophy group 1](image)

**Figure 5.** ECG of ventricular tachycardia (VT) induced in one dog from left ventricular hypertrophy group 1. ECG leads II and $V_{50}$ recorded simultaneously with pairs of epicardial (ep) and endocardial (en) electrograms from the ischemic zone (IZ) and normal zone (NZ). Also recorded were central aortic and left atrial pressure. VT induced during hypertension (left panel) had a cycle length of 170 msec, and VT induced during nitroprusside (right panel) had a cycle length of 220 msec. The same surface ECG and sequence of intracardiac electrograms occurred in both.
blood flow to the ischemic zone, no change in TAT was observed (Table 4). During sequential nitroprusside infusions before or after β-blockade, the magnitude of changes measured in left atrial pressure, echocardiographic left ventricular diastolic dimension, and blood flow to both ischemic and nonischemic zones did not correlate with changes in TAT in LVH group 2 (best r<0.20). Thus, blockade of β-adrenergic influences with metoprolol prevented hypotension-produced prolongation of TAT, suggesting that reflex activation of sympathetic influences to the ischemic zone produced by nitroprusside were responsible.

To examine the effect of β-adrenergic influences on VT, we performed studies on LVH group 3 (Table 5). As in LVH group 2, sequential nitroprusside infusions were separated by metoprolol administration. The effects on TAT were similar to those seen with group 2 (Table 5). The effects on VT are illustrated in Figure 8.

During nitroprusside infusion, the cycle length of VT was prolonged in seven of eight dogs, and VT was not inducible in three and nonsustained in one. Subsequent metoprolol alone prevented VT induction (n=2), rendered VT nonsustained (n=5), or altered the cycle length of VT (Figure 8). Nitroprusside after metoprolol restored sustained VT in one, and three remained inducible; the cycle length of VT was still prolonged in three of these four animals (Figure 8).

**Discussion**

Two major findings are demonstrated by this study. First, endocardial-to-epicardial activation time in acutely ischemic myocardium in dogs with pressure-overload LVH is uniquely responsive to hemodynamic influences. Ventricular activation and the rate of ventricular tachycardia slow with reduction in aortic pressure, and both are accelerated by the reverse. This finding was not observed in normotensive nonhypertrophied ventricles, and in addition, no alteration in MAP resulted in an ability to initiate VT in dogs without LVH. Second, the changes in ventricular activation were eliminated by β-blockade, suggesting that their modulation is caused by adrenergic influence. Unlike ventricular activation, the regulation of the cycle length and inducibility of VT appears to be mediated primarily by effects produced directly by lowering MAP, the mechanism of which is unknown.

**Consideration of the Model**

Several factors, including autonomic influences, myocardial blood flow, and wall stretch, might be implicated as having influence on ventricular activation and conduction and might be active in this model; these might be elicited by either a reduction or an elevation in aortic pressure. In addition, myocardial hypertrophy has been associated with altered cellular and tissue electrophysiological properties, some of which may influence these findings.

Careful attention was directed to changes in wall stretch or preload, as reflected by left atrial pressure and left ventricular end diastolic volume, to examine whether a correlation existed with the changes observed in TAT in the ischemic zone. No correlation was

**TABLE 4. Hemodynamic and Activation Time Response to Metoprolol: Left Ventricular Hypertrophy Group 2**

<table>
<thead>
<tr>
<th></th>
<th>Before metoprolol</th>
<th>After metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before nitroprusside</td>
<td>During nitroprusside</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>123±10</td>
<td>69±4*</td>
</tr>
<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>12±2</td>
<td>9±1</td>
</tr>
<tr>
<td>Transmural normal zone blood flow (ml · min⁻¹ · 100 g⁻¹)</td>
<td>95±9</td>
<td>96±12</td>
</tr>
<tr>
<td>Transmural ischemic zone blood flow (ml · min⁻¹ · 100 g⁻¹)</td>
<td>23±4</td>
<td>19±5</td>
</tr>
<tr>
<td>Ischemic zone blood flow as percent of normal zone flow</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>LV end diastolic diameter (mm)</td>
<td>32±2</td>
<td>27±2*</td>
</tr>
<tr>
<td>Transmural activation time (msec)</td>
<td>Ischemic zone</td>
<td>30±2</td>
</tr>
<tr>
<td></td>
<td>Normal zone</td>
<td>15±2</td>
</tr>
<tr>
<td>Change in ischemic zone activation time (msec)</td>
<td>3 ±1</td>
<td>0 ±1*</td>
</tr>
</tbody>
</table>

LV, left ventricular.
*p<0.05 compared with before nitroprusside.
*p<0.05 compared with before metoprolol.
discovered, with similar changes in wall stretch indexes observed between the LVH and control groups and with changes in these parameters not correlating with the magnitude of change in TAT within the LVH group. This is an argument against either altered preload or other mechanisms of wall stretch as a causative mechanism in producing the electrophysiological changes. Likewise, the magnitude of change in blood flow to normal and ischemic zones in the LVH group 2 during hypertensive and hypotensive interventions did not correlate with changes in TAT, suggesting that the effect was not directly produced by worsening of regional ischemia. Additional evidence that the increase in TAT seen with hypotension was not a result of hypoperfusion is that the intervention that produced the greatest fall in ischemic zone blood flow, nitroprusside infusion after metoprolol administration, prevented the prolongation of activation time. Taken together, it seems unlikely that alteration in ischemic zone blood flow caused by modulation of aortic pressure produced the observed electrophysiological changes.

It is also unlikely that these changes result from a direct pharmacological effect of drugs used to alter MAP, because nitroprusside and nitroglycerin had effects on TAT and VT cycle length similar to those of inferior vena caval occlusion, and phenylephrine and methoxamine had effects similar to those of descending aortic occlusion. The findings with atropine would suggest that parasympathetic influences did not importantly mediate the observed changes in TAT, especially because it is accepted that parasympathetic denervation occurs in the first hour after coronary occlusion and would be complete at the time we performed our measurements. The ability of metoprolol to abolish the changes in activation time in LVH group 2 strongly suggests a direct role for β-adrenergic influences in producing the changes in TAT with alterations in aortic pressure.

Although VT slowing was not prevented during hypotension by metoprolol, and the primary mechanism for this slowing appears to be related to a direct effect of hypotension on the myocardium, a role for reflex alteration of sympathetic neural influence was at least suggested by the divergent responses in TAT and cycle length of VT seen with phenylephrine compared with sympathetic nerve stimulation. During this intervention, the rise in MAP was similar, but changes in cardiac efferent sympathetic nerve activity must be opposite.

This study suggests that in LVH and subacute ischemia, sympathetic influences act to retard conduction, as might have been predicted from previous studies of global sympathectomy in dogs without LVH after 5 minutes of coronary occlusion. However, contrary effects have been seen in other models studied after

---

**TABLE 5. Hemodynamic and Electrophysiological Response to Nitroprusside and Metoprolol: Left Ventricular Hypertrophy Group 3**

<table>
<thead>
<tr>
<th></th>
<th>Before metoprolol</th>
<th>After metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>123±5</td>
<td>57±2*</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>15±1</td>
<td>11±1</td>
</tr>
<tr>
<td>Transmural ischemic zone activation time (msec)</td>
<td>34±3</td>
<td>39±3*</td>
</tr>
</tbody>
</table>

*p<0.05 compared with before nitroprusside.

*p<0.05 compared with before metoprolol.

---

**FIGURE 7.** Graphs showing changes in transmural activation time (TAT) of ischemic zone in left ventricular hypertrophy group 2 during nitroprusside before (left panel) and after metoprolol (right panel). A prolongation of TAT was blocked after metoprolol.
FIGURE 8. Graph showing changes in the cycle length of ventricular tachycardia (VT) in left ventricular hypertrophy group 3 with both nitroprusside and metoprolol. The VT slowed with nitroprusside before and after metoprolol. Metoprolol alone had a variable effect on VT cycle length.

INTERVENTIONS

different durations of coronary occlusion. For example, Martins et al.\(^{14}\) demonstrated that withdrawal of sympathetic influence caused a deterioration in conduction when topical phenol application resulted in regional cardiac sympathectomy, producing increased excitatory threshold and prolongation in the duration of epicardial activation potentials in the first minutes after coronary ligation. In another study of open-chest dogs 3–7 days after coronary occlusion, El-Sherif\(^{21}\) found that conduction across the epicardium overlying a transmural infarction, as detected by a composite electrode system, was improved by sympathetic nerve stimulation. The discordance between our results and these previous studies probably relates to the unique nature of the response of hypertrophied and ischemic myocardium to sympathetic influences or perhaps differences in the method of sympathetic blockade.

The changes in TAT of the ischemic zone during altered MAP appeared to be closely linked to the changes in the cycle length of VT, except after \(\beta\)-blockade with metoprolol. Metoprolol alone, without reduction in aortic pressure, appeared to have a variable effect on the rate of VT but did appear to reduce VT inducibility. In those experiments in which VT remained inducible after metoprolol, however, VT still appeared to slow as MAP was reduced during nitroprusside infusion. Because the VT induced in this model has features consistent with reentry,\(^{7}\) we suspect that conduction must have slowed somewhere in the reentrant circuit during nitroprusside infusion after metoprolol but that this took place in the portion of the circuit that we did not directly record. Although our limited data with sympathetic nerve stimulation appear to support at least some component of direct \(\beta\)-adrenergic influence, the body of our results suggests that other nonsympathetic factors associated with nitroprusside infusion are primarily responsible for modulation of the rate of VT in this model. In addition to factors discussed above\(^{14–20}\) for TAT, deterioration of blood flow in the ischemic zone after metoprolol must be considered one explanation for the slowing of VT, although we cannot explain an absence of blood flow change when TAT was delayed. This would be possible if alteration of ischemic zone blood flow during an intervention occurs nonhomogeneously and is variable between small neighboring regions of myocardium within the ischemic zone. Additional experiments in which detailed mapping of the reentry circuit is combined with detailed exploration of regional blood flow would be useful in excluding this possibility. It is conceivable that other humoral factors that are altered during nitroprusside administration, such as the renin–angiotensin system, may also play a role.

Relation to Other Studies in this Model

This study contributes to knowledge of this model of VT associated with pressure-overload LVH after coronary occlusion. The initial description of this model of pressure-overload ventricular hypertrophy\(^{5}\) documented an exaggerated frequency of sudden cardiac death early after closed-chest circumflex coronary occlusion. It was then discovered that after open-chest infarction, dogs with LVH were unique in their vulnerability to induction of rapid monomorphic VT.\(^{5}\) Compared with nonhypertrophied controls, dogs with LVH had an excessively prolonged endocardial-to-epicardial TAT in the ischemic zone, and this was postulated to provide conduction delay needed for supporting reentry VT.\(^{5}\) In fact, when transmural conduction delay within the ischemic zone was greatly prolonged by premature stimuli, VT was induced.\(^{5}\) The current study demonstrates, however, that the changes in TAT of the ischemic zone may be blocked by metoprolol, whereas the cycle length of the VT continues to prolong during hypotension. Therefore, although transmural conduction delay is not always linked to VT cycle length, the present data do not exclude a reentry mechanism for VT in this model. Preliminary examinations of this VT with a detailed computer-aided epicardial and transmural mapping system have shown conduction delay and activation patterns suggesting that reentry, often epicardial in location, is present (unpublished results). Thus,
as has been suggested by the present experiments, reentry may be the mechanism of this VT, which is altered by changes in MAP, but the transmural conduction changes might not be causally related.

**Implications**

This study enhances our knowledge of the electrophysiological substrate that is responsible for arrhythmogenesis in this canine model of ischemia in LVH caused by sustained hypertension. This model resembles heart disease commonly seen in patients with hypertension in both the level of hypertension developed and the degree of LVH. It also appears to mimic the exaggerated incidence of sudden cardiac death experienced after myocardial infarction by patients with LVH. Rapid monomorphic VT, a nearly universal feature of this model, is often the pre fibrillatory event recorded in human victims of sudden cardiac death and is inducible in survivors who subsequently undergo electrophysiological testing. A better understanding of this model may allow improved evaluation and therapy in patients with this disorder. Additional studies using β-blockade demonstrate that the dramatic increases in postinfarction mortality in this animal model can be reversed independently of reduction in infarct size. These results suggest that the mechanism by which β-blockers improve sudden death mortality in patients after myocardial infarction may be by their effects on hypertrophied and ischemic myocardium.

**Acknowledgments**

The authors wish to thank Bruce McCallum, Mary Miller, and Laura Hingtgen for skilled technical assistance and Nancy Davin for expert secretarial assistance.

**References**

13. Larsen RJ: *Statistics for the Health Sciences*. Columbus, Ohio, Charles E. Merrill, 1975, pp 206–259
Hemodynamic and reflex sympathetic control of transmural activation and rate of ventricular tachycardia in ischemic and hypertrophic ventricular myocardium of the dog.

J R Hopson and J B Martins

Circulation. 1992;86:618-627

doi: 10.1161/01.CIR.86.2.618

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/86/2/618