The effect of chemical ablation of the endocardium on ventricular fibrillation threshold*

RALPH J. DAMIANO, JR., M.D., PETER K. SMITH, M.D., HENRY F. TRIPP, JR., M.D.,
TETSUO ASANO, M.D., KENT W. SMALL, M.D., JAMES E. LOWE, M.D.,
RAYMOND E. IDEKER, M.D., PH.D., AND JAMES L. COX, M.D.

ABSTRACT The purpose of this study was to examine the effects of ablation of the superficial endocardium and Purkinje network on left ventricular fibrillation threshold. Lugol's solution was applied through small ventriculotomies to the left and right ventricular endocardium of 10 dogs on cardiopulmonary bypass. Two control groups of five animals each underwent either endocardial application of saline or epicardial application of Lugol's solution. Ventricular fibrillation threshold was measured before and after each intervention by the single-stimulus technique. Application of Lugol's solution to the endocardium resulted in a 102 ± 15% increase in ventricular fibrillation threshold from a control value of 26 ± 2 to 53 ± 6 mA (p < .005). In two animals, ventricular fibrillation could not be initiated postoperatively. In the control groups, there were no significant changes in ventricular fibrillation threshold. Histologic examination revealed that Lugol's solution obliterated less than 0.5 mm of superficial endocardium while sparing the adjacent myocardium. Electrophysiologic and rheologic data confirmed the discrete nature of the chemical injury. Thus ablation of the superficial ventricular endocardium with Lugol's solution results in a profound increase in the ventricular fibrillation threshold with only minimal tissue destruction. Circulation 74, No. 3, 645–652, 1986.

VENTRICULAR FIBRILLATION is a lethal arrhythmia and an important cause of sudden death.1 At present, there are no reliable methods to predict or prevent its occurrence, not only because of the apparent random and chaotic nature of fibrillation but also because the precise mechanisms of its initiation, maintenance, and termination are unknown. However, the endocardium, particularly the Purkinje network, has been shown to play an important role in the genesis of reentrant tachyarrhythmias.2–4 Various arrhythmias that result from abnormal automaticity have also been shown to originate in Purkinje tissue.5–11 Although the endocardium has been documented both clinically and experimentally to be an important substrate in ventricular tachycardia, its role in ventricular fibrillation is less clear.12–18 Nevertheless, transmural recordings during ventricular fibrillation have documented endocardial to epicardial spread of activation with variable block, implying an endocardial origin of many of the activation fronts that maintain the arrhythmia.19

The purpose of this study was to examine the effect of ablation of the superficial endocardium and Purkinje fiber network on the ability to initiate ventricular fibrillation. Lugol's solution, a concentrated iodine solution, has an affinity for glycogen. It has been demonstrated to stain and ablate both Purkinje fibers and endocardial tissue.20–22 In this study, the electrophysiologic effects of the endocardial application of Lugol's solution on ventricular fibrillation threshold were examined. In addition, the rheologic and histologic changes induced by this procedure were also investigated.

Methods
Twenty adult mongrel dogs weighing 25 to 35 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg) and maintained on a constant-drip infusion of 2 mg/min throughout the study. Ventilation was maintained via a cuffed endotracheal
tube and a Bennett MA-1 volume-cycled respirator. A median sternotomy was performed and the heart was suspended in a pericardial cradle (figure 1). Central aortic and femoral arterial pressures were monitored continuously with fluid-filled catheters and Stratham P23ID pressure transducers. Central temperature was measured in the inferior vena cava with a Swan-Ganz catheter connected to a thermal dilution cardiac output computer. After systemic heparinization, the azygos vein was ligated and both vena cavae were cannulated individually for cardiopulmonary bypass. The femoral artery was cannulated for arterial perfusion. The animals were placed on total cardiopulmonary bypass and the right and left ventricles were vented for decompression. Aasquignous priming solution and a Shiley Model 100-A bubble oxygenator were used. The animals were perfused at flow rates of 2.0 to 2.5 liters/min/m² and mean aortic pressure was maintained at 70 to 100 mm Hg throughout the study. All data were obtained in the empty, beating heart. Potassium, sodium, ionized calcium, and arterial blood gases were obtained before cardiopulmonary bypass and before each period of data acquisition and were maintained within physiologic limits.

Limb lead II of the standard electrocardiogram was monitored continuously. Bipolar epicardial stainless steel recording electrodes were sutured to the right and left ventricular free walls. A specially designed epicardial plaque was used for the determination of ventricular fibrillation threshold. Silver wire electrodes were fixed in a thin silicone rubber plaque so that the interelectrode and intraelectrode distances were 1.5 cm. All electrograms were filtered with high-gain bioelectric amplifiers (Hewlett Packard 8811A) with a high-pass frequency of 0.5 Hz and a low-pass frequency of 1 kHz. All physiologic signals were recorded continuously on magnetic tape (Hewlett Packard 3520B) at a speed of 3.25 inches/sec. Signals were displayed on an eight-channel oscilloscope (Hewlett Packard 78309A) and reproduced on paper by an eight-channel Gould 2800 strip-chart recorder. In five animals, unipolar plunge needle electrodes were placed in the anterior left ventricular free wall to monitor transmural myocardial activation. These electrodes were con-structed as described previously. Electrical data from the intramural plurale electrodes were recorded on a 32-channel Ampex analog tape recorder and displayed at a paper speed of 250 mm/sec on a Siemens-Elema minograph.

Radioactive carbonized tracer microspheres, 9 to 12 μm diameter (125I, 14C, 53Sr, and 46Sc) were used to determine regional myocardial blood flow. Flow determinations were made by injecting 3 × 10⁶ premixed microspheres into the arterial perfusion cannula while a reference sample of arterial blood was withdrawn concomitantly from the central aortic catheter at 14 ml/min. Myocardial blood flow was determined by the method of Rudolph and Heymann. After the study, the hearts were fixed in formalin, divided into 0.5 to 2 g sections, and counted in a Packard multichannel gamma spectrometer. Specially designed computer programs and a PDP 11/34 computer were used to determine myocardial blood flow (ml/min/g).

Left ventricular fibrillation thresholds were determined by the single-stimulus technique. A constant-current stimulus driven by a specially designed computer program delivered a train of 10 S₁ stimuli at twice diastolic threshold with a basic cycle length of 350 msec. A premature stimulus, the S₂, was then introduced 200 msec after the final S₁ paced beat. The S₂ pulse width was 5 msec. The initial strength of the S₂ was 10 mA and current strength was monitored on-line with an oscilloscope. Diastole was scanned in 5 msec decrements until S₂ became refractory. This process was repeated, each time increasing S₂ current strength by 2 mA, until ventricular fibrillation was initiated. The dogs were defibrillated within 10 to 20 sec after the onset of the arrhythmia and were allowed to recover for 20 min between each threshold determination. Electrolytes and arterial blood gases were measured during the recovery period and any abnormality was corrected. This protocol was repeated until two thresholds were recorded within 2 mA of each other.

**Experimental protocol.** After institution of normothermic cardiopulmonary bypass, control data were acquired. Myocardial blood flow was measured at a heart rate of 150 beats/min during left ventricular pacing. Left ventricular fibrillation thresholds and repetitive response thresholds were then determined. In five dogs, transmural myocardial activation was measured by plunge electrodes during ventricular pacing from two bipolar epicardial electrodes located within 2 cm of the plunge electrodes. Small anterior left and right ventriculotomies were then performed.

The animals were divided into four groups. In the first group (n = 10), the endocardial surfaces of both ventricles were painted with Lugol’s solution. The solution consisted of 5 g of organic iodine and 10 g of potassium iodide diluted in 100 ml of distilled water. In the second group (n = 5), the endocardial surfaces were painted with saline. In the third group (n = 5), the epicardial surfaces of both ventricles were painted with Lugol’s solution. The fourth group (n = 5) underwent obliteration of the atrophicventricular (AV) node with 1% formalin solution with resultant complete heart block. This was accomplished by injection of the formalin solution with a tuberculin syringe into the region of the proximal His bundle. Identical ventriculotomies were performed in all four groups. These sham or control groups were included to ensure that any physiologic changes observed during the study were caused by the specific effect of Lugol’s solution on the endocardium and not by some other aspect of the experimental protocol.

The ventriculotomies were closed with a continuous monofilament suture, and the animals were allowed to recover for 30 min. Myocardial blood flow was determined again during ventricular pacing at a heart rate of 150 beats/min. Transmural myocardial activation was recorded as previously described and
ventricular fibrillation thresholds were determined again by the single-stimulus technique.

After the completion of each study, the animals were killed and the hearts were fixed in formalin. The ventricles were sectioned for histologic evaluation and for regional myocardial blood flow determination.

To determine the long-term histologic effects of Lugol’s solution, one dog underwent a sterile operative procedure. A right thoracotomy was performed and the animal was placed on total cardiopulmonary bypass, as described above. The right ventricle was painted with Lugol’s solution. The chest was closed and the animal was allowed to recover for 5 days. The heart was then removed and sectioned for histologic examination.

All statistical analyses were performed with Student’s t test for paired and unpaired data.

Results

Histologic studies. The application of Lugol’s solution to the ventricular endocardium resulted in a thin layer of cell necrosis and inflammation confined to the endocardial surface (figure 2). This layer measured less than 0.5 mm in depth, consisting of only a few cell layers. The adjacent subendocardium and the remainder of the myocardium extending to the epicardium showed no evidence of injury.

The heart from each animal was carefully examined after the studies were completed. Every heart showed complete and uniform staining of the endocardial surface of both ventricles by the Lugol’s solution. Histologic sections from the hearts in the short-term studies revealed that the staining resulting from the application of Lugol’s solution was distributed uniformly over the endocardial surface and was limited to its most superficial cell layers. Thus the application of Lugol’s solution resulted in a uniform, complete, and discrete rim of superficial endocardial necrosis that did not involve the overlying cardiac muscle histologically.

Physiologic effects. All animals were supported on cardiopulmonary bypass throughout the study. Arterial blood pressure, systemic temperature, arterial blood gases, serum sodium, potassium, and ionized calcium were measured in all groups. The results, before and after the application of Lugol’s solution, are listed in table 1. There were no significant differences in any of the measured variables before and after the application of Lugol’s solution.

Effects on regional myocardial blood flow. Regional myocardial blood flow was measured before and after either Lugol’s solution or saline was administered to the endocardium (table 2). Total left ventricular myocardial blood flow increased by a similar magnitude in both groups, 23 ± 18% in the group receiving saline and 31 ± 10% in the group receiving Lugol’s solution (p = NS). This suggests that the increase in blood flow was independent of the administration of the Lugol’s solution to the endocardium and was the result of the experimental protocol and cardiopulmonary bypass itself. However, the transmural distribution of myocardial blood flow was significantly altered by the endo-

FIGURE 2. Histologic sections of the right ventricle examined 5 days after endocardial application of Lugol’s solution. The heart was fixed in formalin, mounted in paraffin, sectioned, and stained with hematoxylin and eosin.
Endocardial application of Lugol’s solution. Left ventricular subendocardial blood flow increased proportionately more than subepicardial flow in the group receiving Lugol’s solution, resulting in an increase in the endocardial to epicardial flow ratio from 1.12 ± .04 to 1.36 ± 0.06 (p < .005). In contradistinction, the endocardial to epicardial flow ratio in the saline-treated animals did not change significantly, falling from 1.10 ± 0.06 to 0.90 ± 0.04 (p = NS).

Right ventricular myocardial blood flow also increased by a similar magnitude in both groups. However, the right ventricular endocardial/epicardial flow ratio was not significantly altered by application of either saline or Lugol’s solution to the endocardium.

**Electrophysiologic effects**

**Effects on AV conduction.** All animals treated with bi-ventricular endocardial Lugol’s solution developed complete heart block. In the animals that received endocardial saline or epicardial Lugol’s solution, there was no evidence of AV conduction disturbance.

**Transmural activation.** To examine the effects of endocardial Lugol’s solution on transmural electrical activity, a unipolar plunge needle electrode was placed in the anterior left ventricular free wall within 2 cm of the stimulating plaque. Each transmural needle shaft contained eight electrodes with an interelectrode distance of 0.5 mm. The needle electrodes were fixed to the endocardium, the first intramural electrode being 1.5 mm from the ventricular cavity. Ventricular pacing at a basic cycle length of 400 msec was performed from the stimulating plaque. The pacing electrode was placed as near as possible to the plunge needle electrode to ensure that the conducted impulse propagated through the myocardium and did not involve the specialized conduction tissue (i.e., Purkinje network). The conduction time was defined as the interval between the pacing artifact and local activation. In the five animals examined, there were no differences in the amplitude or slope of the fastest deflection, conduction time, or activation sequence after application of Lugol’s solution. Transmural unipolar electrograms from one animal are shown in figure 3. The transmural activation sequence, with the epicardium activating several milliseconds before the endocardium, was unchanged. The conduction time was not altered significantly even at the most subendocardial electrode. Thus normal transmural conduction was preserved despite the ablation of the superficial endocardium and the Purkinje network. The absence of changes in the slope and amplitude of the fastest deflection of the unipolar electrogram, even at the most subendocardial electrode, attests to the discrete nature of the endocardial injury.

**Ventricular fibrillation threshold.** The changes in ventricular fibrillation threshold after endocardial application of Lugol’s solution were dramatic (figure 4). Every animal showed a marked increase in ventricular fibrillation threshold. In two of the 10 animals, fibrillation could not be induced after Lugol’s application despite the use of stimulus strengths up to 80 mA. For the entire group, the mean left ventricular fibrillation threshold increased from 26 ± 2 to 53 ± 6 mA, a 102

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**TABLE 1**

**Physiologic variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before</th>
<th>After</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>68 ± 2</td>
<td>69 ± 3</td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.7 ± 0.1</td>
<td>37.7 ± 1</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.48 ± 0.02</td>
<td>7.44 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Pco₂ (mm Hg)</td>
<td>192 ± 17</td>
<td>179 ± 14</td>
<td></td>
</tr>
<tr>
<td>Pc₄₂ (mm Hg)</td>
<td>36 ± 2</td>
<td>29 ± 2</td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>145 ± 2</td>
<td>149 ± 1</td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>3.9 ± 0.2</td>
<td>3.6 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>0.99 ± 0.04</td>
<td>1.04 ± 0.03</td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as mean ± SEM.

There were no significant differences between values obtained before and after application of Lugol’s solution.

**TABLE 2**

**Regional myocardial blood flow (ml/min/g, ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
<th>p value</th>
<th></th>
<th>Before</th>
<th>After</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV total</td>
<td>0.97 ± 0.06</td>
<td>1.26 ± 10</td>
<td>.005</td>
<td>Saline</td>
<td>1.37 ± 0.09</td>
<td>1.70 ± 0.27</td>
<td>NS</td>
</tr>
<tr>
<td>LV endocardium</td>
<td>1.04 ± 0.07</td>
<td>1.47 ± 0.12</td>
<td>.001</td>
<td>LV</td>
<td>1.44 ± 0.07</td>
<td>1.60 ± 0.22</td>
<td>NS</td>
</tr>
<tr>
<td>LV epicardium</td>
<td>0.93 ± 0.06</td>
<td>1.08 ± 0.08</td>
<td>.05</td>
<td>LV endo/epi ratio</td>
<td>1.12 ± 0.04</td>
<td>1.36 ± 0.06</td>
<td>.005</td>
</tr>
<tr>
<td>RV total</td>
<td>0.78 ± 0.06</td>
<td>0.87 ± 0.11</td>
<td>NS</td>
<td>RV</td>
<td>1.10 ± 0.06</td>
<td>0.90 ± 0.04</td>
<td>NS</td>
</tr>
<tr>
<td>RV endocardium</td>
<td>0.71 ± 0.06</td>
<td>0.84 ± 0.16</td>
<td>NS</td>
<td>RV</td>
<td>1.12 ± 0.10</td>
<td>1.41 ± 0.33</td>
<td>NS</td>
</tr>
<tr>
<td>RV epicardium</td>
<td>0.84 ± 0.10</td>
<td>0.91 ± 0.10</td>
<td>NS</td>
<td>RV endo/epi ratio</td>
<td>0.90 ± 0.08</td>
<td>0.90 ± 0.08</td>
<td>NS</td>
</tr>
</tbody>
</table>

LV = left ventricular; RV = right ventricular.
\textbf{FIGURE 3.} Transmural unipolar electrograms recorded before (PRE) and after (POST) application of Lugol's solution in one animal. The conduction time (msec), the interval between the pacing artifact and local activation, is displayed immediately to the right of the pacing artifact for each electrogram.

\textbf{FIGURE 4.} Ventricular fibrillation thresholds before (PRE) and after (POST) endocardial application of Lugol's solution. Means ± SEM are represented by the larger circles. In two of the 10 animals, fibrillation could not be induced after application of Lugol's solution and for the purpose of data analysis these animals were assigned threshold values of 80 mA.

\textbf{FIGURE 5.} Ventricular fibrillation thresholds for the animals treated with saline, epicardial (EPI) Lugol's solution, and endocardial (ENDO) Lugol's solution. All values are represented as a percentage of control ventricular fibrillation threshold. Only the group that received endocardial Lugol's solution showed a change that was significantly different from control values.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Transmural unipolar electrograms recorded before (PRE) and after (POST) application of Lugol's solution in one animal. The conduction time (msec), the interval between the pacing artifact and local activation, is displayed immediately to the right of the pacing artifact for each electrogram.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Ventricular fibrillation thresholds before (PRE) and after (POST) endocardial application of Lugol's solution. Means ± SEM are represented by the larger circles. In two of the 10 animals, fibrillation could not be induced after application of Lugol's solution and for the purpose of data analysis these animals were assigned threshold values of 80 mA.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Ventricular fibrillation thresholds for the animals treated with saline, epicardial (EPI) Lugol's solution, and endocardial (ENDO) Lugol's solution. All values are represented as a percentage of control ventricular fibrillation threshold. Only the group that received endocardial Lugol's solution showed a change that was significantly different from control values.}
\end{figure}

\textbf{LABORATORY INVESTIGATION—ARRHYTHMIA}

\pm 15\% increase (p < .005) (figure 5). In contrast, there were no significant changes in ventricular fibrillation thresholds in the sham or control groups (figure 5). Moreover, in the five animals that underwent AV node ablation alone, ventricular fibrillation thresholds were unaltered, 23 ± 4 to 24 ± 5 mA (p = NS).

\textbf{Discussion}

Several previous studies have stressed the importance of the endocardial Purkinje system in ventricular arrhythmias, particularly ventricular tachycardia.\textsuperscript{2-7,12-18} However, the precise electrophysiologic mechanisms involved in the initiation and perpetuation of ventricular fibrillation are unknown. Worley et al.,\textsuperscript{19} using closely spaced bipolar intramural electrodes, demonstrated that after the initial 1 to 2 min of ventricular fibrillation, the rate of activation is much faster at the endocardial level than at the epicardium, with variable degrees of block between endocardium and epicardium. This observation implies that the endocardium may be the origin of many of the electrical wavefronts that sustain the arrhythmia. Janse et al.\textsuperscript{5} documented difficulty fibrillating the isolated heart when the endocardium had been ablated with a phenol solution. The data in the present study are consistent with Janse's observations and demonstrate the importance of the superficial endocardium and parietal Purkinje system in the initiation and maintenance of ventricular fibrillation.

In this study, Lugol's solution was used to ablate the
superficial endocardium. Completeness of this destruction was documented in every animal by careful histologic examination of the ventricles after each study. Ablation of the conduction system was documented by the complete heart block that developed in each animal and the slow resultant idioventricular rhythm.

The destructive action of Lugol’s solution was confined to the endocardium, ablatting only a thin layer less than 0.5 mm thick. There was no histologic evidence of injury to the overlying myocardium. Rheologic and electrophysiologic data also support the discrete nature of the injury incurred with Lugol’s solution. Examination of regional myocardial blood flow showed no evidence of subendocardial muscle injury. In fact, subendocardial blood flow increased in relation to subepicardial flow after application of the Lugol’s solution. This increase in endocardial/epicardial blood flow ratio did not occur in the control groups. The transmural redistribution of blood flow may represent a reactive hyperemic response to the localized superficial endocardial injury caused by the Lugol’s solution.

Electrophysiologic data revealed no significant changes in transmural electrical activity or wavefront propagation after the endocardial application of Lugol’s solution. Unipolar electrograms recorded within 1.5 mm of the endocardial surface showed no significant change in the amplitude or slope of the fastest deflection. Transmural conduction time during epicardial pacing from a point close to the plunge needle electrodes was unaltered. There was also no electrophysiologic evidence of local tissue injury in the overlying myocardium. Thus the histologic, rheologic, and electrophysiologic data demonstrate that Lugol’s solution specifically ablates the thin layer of superficial endocardium harboring the parietal Purkinje system but preserves the physiologic characteristics of the overlying myocardium.

Ablation of the superficial endocardium resulted in a dramatic increase in ventricular fibrillation threshold as determined by the single-stimulus technique. Data from the control groups — involving endocardial application of saline, epicardial application of Lugol’s solution, and selective AV node ablation — confirmed that the experimental protocol, the operative procedure, cardiopulmonary bypass, the nonspecific ablation of myocardium, and the creation of AV block played no role in the increase in the ventricular fibrillation threshold that occurred after superficial endocardial ablation with Lugol’s solution.

As with any experimental observation, the applicability of these findings to the clinical setting is unknown. For example, the relationship between ventricular fibrillation threshold as measured by the primary-stimulus technique and the clinical occurrence of spontaneous ventricular fibrillation is uncertain. However, various investigators have documented that ventricular fibrillation threshold measured by this technique correlates well with clinical factors known to enhance vulnerability to ventricular fibrillation.25–28 Thus, although the primary stimulus technique has been verified as a reproducible and accurate means of determining ventricular fibrillation in experimental animals, the mechanisms of ventricular fibrillation initiation clinically may be different. It has been suggested that fibrillation induced by the primary-stimulus technique originates from a small region around the stimulating electrodes and involves local reentrant activity.29 The origin of this local reentrant activity, whether endocardial, myocardial, or epicardial, has never been clearly demonstrated. Although this represents a limitation of the technique, it is a limitation common to most experimental methods used to study the initiation of ventricular fibrillation. Furthermore, this limitation does not negate the data in the present study documenting that superficial endocardial ablation dramatically increases ventricular fibrillation threshold.

It is interesting that Janse et al.3 showed that destruction of the subendocardium with phenol resulted not only in an increase in the fibrillation threshold but also in the inability to induce subsequent fibrillation. The difference between our results and theirs may be due to several factors. The Lugol’s solution used in our study caused a discrete superficial injury that was confined to the endocardium. This injury was likely more localized and less destructive than that caused by the phenol solution. In addition, the genesis of ventricular fibrillation by the single-stimulus technique may be different from that of other experimental preparations. Further studies are needed to define the precise origin of ventricular fibrillation and to determine the electrophysiologic mechanisms responsible for both spontaneous ventricular fibrillation and that initiated by a premature stimulus.

Precise delineation of the anatomic endocardial substrate that is ablated by Lugol’s solution also requires further investigation. This substrate may be only the superficial Purkinje network that is clearly abolished by the Lugol’s solution, as evidenced both by histologic data and the resultant complete heart block in these animals. Purkinje fibers may play a role by either serving as the fast conduction pathways necessary for
fibrillation or by providing the requisite electrical inhomogeneity needed to develop and sustain the arrhythmia. Moreover, under certain conditions, automaticity and triggered automaticity have been induced within Purkinje fibers. Although these mechanisms may not have played a major role in the initiation or maintenance of ventricular fibrillation in the animals with nonischemic myocardium in our study, their potential contribution cannot be excluded. The cholinergic fibers located in the subendocardium represent another substrate that may influence the vulnerability to ventricular fibrillation. Although cholinergic innervation of ventricular myocardium is sparse, innervation of the ventricular conducting system located primarily on the endocardium is abundant. However, experimental evidence suggests that ablation of cholinergic tone would actually decrease rather than increase the ventricular fibrillation threshold, and therefore it seems unlikely that this would explain our findings.

Initiation of ventricular fibrillation requires both electrical inhomogeneity and a critical mass of available conducting myocardium. Thus it is theoretically possible that the increase in ventricular fibrillation threshold caused by endocardial Lugol's application occurs because of a decrease in myocardial mass secondary to concomitant ablation of adjacent subendocardial tissue. However, only an extremely thin (<0.5 mm) layer of superficial endocardium is ablated by the Lugol's solution. Previous data from our laboratory suggest that at least 20 g of myocardium must be ablated before the ventricular fibrillation threshold is increased. To eliminate ventricular fibrillation and abolish its inducibility, an even larger amount of myocardium would have to be depolarized or ablated. Moreover, the ablation of a similar amount of epicardial tissue with Lugol's solution had no effect on the ventricular fibrillation threshold. Thus the concept of critical mass would seem to be of little importance in terms of the mechanism by which endocardial Lugol's application increased the ventricular fibrillation threshold in the present study. On the contrary, our data suggest that ablation of the Purkinje system is most likely responsible for the increase in ventricular fibrillation threshold after endocardial Lugol's application.

As mentioned above, one must exercise caution in transferring these experimental findings to the clinical setting. However, at present there is no surgical procedure available for the treatment of primary ventricular fibrillation, i.e., fibrillation that is not preceded by at least a few cycles of ventricular tachycardia. The reason for this deficiency is that a "site of origin" for ventricular fibrillation cannot be determined by the electrophysiologic techniques used to localize the arrhythmogenic myocardium responsible for ventricular tachycardia. Our results suggest that superficial ablation of the endocardial Purkinje system may represent a rational goal in patients with primary ventricular fibrillation when the arrhythmia is refractory to medical therapy.

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