Facilitation of lethal ventricular arrhythmias by therapeutic digoxin in conscious post infarction dogs

The proarrhythmic potential of digoxin, administered in a therapeutic dosage regimen, was evaluated in conscious dogs in the subacute phase of myocardial infarction. In this evaluation, digoxin (0.0125 mg/kg/day intravenously) or vehicle were administered to conscious dogs for periods of 5 to 7 days, commencing 4 to 5 days after anterior myocardial infarction. Before treatment, programmed ventricular stimulation failed to initiate ventricular tachycardia in 26 post infarction dogs. After treatment, programmed stimulation initiated ventricular tachyarrhythmias in only 1 of 13 digoxin-treated dogs (1.36 ± 0.17 ng/ml serum digoxin) and in 0 of 13 vehicle-treated dogs. However, the incidences of early ventricular fibrillation (4 of 10 digoxin vs 0 of 12 vehicle; p < 0.05) and of 24-hour mortality (6 of 10 digoxin vs 2 of 12 vehicle; p < 0.05) occurring in response to the development of posterolateral ischemia in the presence of previous anterior myocardial infarction was significantly greater in digoxin-treated (1.47 ± 0.19 ng/ml serum digoxin) than in vehicle-treated animals. These findings suggest an enhanced susceptibility toward the development of ischemia-related lethal arrhythmias in the presence of therapeutic digoxin serum concentrations early after myocardial infarction, which is not predicted by programmed ventricular stimulation testing. (Am Heart J 111:883, 1986.)


Considerable uncertainty surrounds the use of digoxin in patients with ischemic myocardial injury. Several large nonrandomized clinical studies have attempted to evaluate the potential deleterious effects of digitalis therapy on survival after acute myocardial infarction, but have yielded conflicting and equivocal results. Experimental studies conducted to date suggest an enhanced myocardial sensitivity to the arrhythmogenic actions of digitalis preparations in the settings of myocardial ischemia and/or myocardial infarction. However, all previous experimental studies invariably have employed the rapid administration of toxic concentrations of digitalis preparations in assessing myocardial sensitivity, thereby limiting the relevance of conclusions drawn from such studies to the clinical situation.

Previously, this laboratory has described a conscious canine model for the study of sudden coronary death precipitated by the development of ischemia at a site distant from an area of previous myocardial infarction. More recent studies have demonstrated a predictive relationship between susceptibility to the initiation of ventricular tachyarrhythmias by programmed ventricular stimulation and vulnerability to the development of lethal ventricular arrhythmias in response to a subsequent ischemic episode in this conscious post infarction dog model. This relationship permits the identification of post infarction animals at low risk to the development of ischemia-related malignant ventricular arrhythmias via prior programmed ventricular stimulation testing. In the present investigation, post infarction dogs which were determined to be at a low risk for the development of ischemia-induced lethal arrhythmias were employed to evaluate the arrhythmogenic potential of the digitalis glycoside, digoxin, administered in a therapeutic dosing regimen.

METHODS

Surgical preparation. Male mongrel dogs (14.0 to 19.0 kg) were anesthetized with intravenous sodium pentobarbital, 30 mg/kg. The dogs were ventilated with room air...
Fig. 1. Conscious post infarction canine model. On the day of surgical preparation, anterior myocardial ischemic injury (demonstrated by the broken line) was produced by a 2-hour occlusion of the left anterior descending coronary artery, followed by reperfusion through a critical stenosis. An epicardial bipolar electrode (A) was sewn onto the left atrial appendage for atrial pacing, and a plunge bipolar electrode (B) was inserted into the interventricular septum, adjacent to the site of occlusion, for the determination of ventricular excitation threshold and refractory period, as well as for the delivery of programmed ventricular extrastimuli. Plunge bipolar electrodes were inserted into normal, noninfarcted myocardium (C) and into potentially infarcted myocardium (D) for the recording of local activation, and for the construction of ventricular strength-interval curves. The bared tip of an insulated silver wire (E) was inserted into the lumen of the left circumflex coronary artery, and the wire was sutured onto the surface of the heart.

An epicardial bipolar electrode (1 mm diameter silver electrodes embedded 3 mm apart in acrylic) was sutured to the left atrial appendage for atrial pacing. A bipolar plunge electrode (25-gauge insulated stainless steel wire, 5 mm in length, 2 mm apart) was sutured into the interventricular septum adjacent to the right ventricular outflow tract for the determination of ventricular excitation threshold, ventricular refractory period, and for the introduction of ventricular extrastimuli during programmed stimulation. Two short (2 to 3 mm) stainless steel bipolar plunge electrodes were used for the measurement of ventricular activation times and for the construction of ventricular strength-interval curves. One short bipolar electrode was implanted in the distribution of the left anterior descending coronary artery distal to the site of occlusion (IZ, infarct zone), while a second electrode was implanted in the left circumflex coronary artery distribution (NZ, normal zone). A 3 mm section of bared insulated 30-gauge silver wire was inserted through the wall and to the lumen of the left circumflex coronary artery and was sutured in place on the surface of the heart. Silver disc electrodes were implanted subcutaneously. The surgical incision was closed and the animals were allowed to recover from surgical anesthesia. The animals received ampicillin, 10 mg/kg subcutaneously twice daily, during their post infarction convalescence. The essential experimental features of this preparation are illustrated in Fig. 1.

Experimental protocol. Post infarction dogs were returned to the laboratory 4 to 5 days after surgical preparation. Electrophysiologic testing and programmed ventricular stimulation were performed while the animals were conscious, unsedated, and resting comfortably in a sling. Only post infarction dogs that were not susceptible to the initiation of ventricular tachycardia during initial programmed stimulation testing were entered into the present investigation. Previous work in this laboratory has shown that post infarction dogs that are resistant to the induction of ventricular tachycardia by programmed stimulation are at "low risk" toward the development of lethal ventricular arrhythmias in response to the subsequent development of posterolateral ischemia (i.e., ischemia at a site distant from the area of previous myocardial infarction).17

After initial electrophysiologic testing, post infarction dogs were randomized to treatment with either digoxin (n = 13, 0.0125 mg/kg/day intravenous Lanoxin, administered in the afternoon as a single infusion via the jugular vein, for 5 to 7 consecutive days) or with vehicle (n = 13, 0.0125 mg/kg/day intravenous saline, administered as a single afternoon infusion, for 5 to 7 consecutive days). Daily morning blood samples were obtained by peripheral venipuncture from the first six digoxin-treated animals for the characterization of the serum digoxin time course profile. Morning venous blood samples were obtained from all digoxin- and vehicle-treated animals for the determination of serum potassium and digoxin concentrations on the day of repeat electrophysiologic testing.

After the appropriate treatment periods, digoxin- and vehicle-treated dogs were subjected to repeat electrophysiologic study and programmed ventricular stimulation in the conscious, unsedated state. Immediately thereafter, digoxin-treated (n = 10) and vehicle-treated (n = 12) dogs were entered into the protocol for left circumflex (LCX)
coronary artery intimal injury. Technical failures associated with the latter protocol (fractured or improperly positioned LCX wire, n = 3; two digoxin- and one vehicle-treated) and lethal responses to programmed stimulation (n = 1) account for the reduction in the number of animals entered into the protocol for LCX coronary artery injury.

Electrophysiologic studies and programmed electrical stimulation. Animals were studied while they were conscious, unedsated, and resting comfortably in a sling. ECG intervals and electrophysiologic parameters were determined immediately before programmed stimulation testing. ECG intervals were measured during sinus rhythm. A corrected QT interval (QTc = QT in msec/(R-R in sec)^12) was determined during sinus rhythm, while a paced QT interval was determined during atrial pacing (2.5 Hz). Ventricular excitation thresholds, refractory periods, and activation times were determined during atrial pacing (2.5 Hz). The ventricular excitation threshold was defined as the minimum required to produce a conducted ventricular beat at a stimulus duration of 4 msec delivered 300 msec after the R wave of the lead II ECG. The ventricular refractory period was the longest R-to-stimulus interval at which a 2x threshold stimulus (4 msec duration) failed to produce a conducted ventricular beat. Normal zone and infarct zone ventricular activation times, the intervals between the Q wave of the lead II ECG, and the largest deflection of the local ventricular electrograms (Q-EG), were measured on a Tektronix model 5111 oscilloscope. Ventricular strength-interval curves were constructed in normal and infarcted myocardium by a modification of a previously reported method.14 An extrastimulus (S2) is introduced in late diastole at a minimum milliampere for eliciting a ventricular response (V2) during a basic V1-V1 drive cycle length of 400 msec (heart rate of 150 bpm) in the conscious dog. The current for the drive beats is held constant throughout the determination at twice the minimum diastolic threshold for excitability. The coupling interval of S1 is then decreased incrementally until S1 fails to elicit a V2. When S1 fails to elicit a V2, the milliampere of S1 is increased until a V2 is elicited, and the coupling interval is decreased until S1 again fails to elicit a V2. This sequence is repeated until a ventricular effective refractory period (ERP) is reached at a maximum current of 4 mA. The ERP, therefore, is defined as the longest S1-S2 interval that fails to elicit V2 at 4 mA. The relative refractory period (RRP) is defined as the longest coupling interval along the strength-interval curve at which the current required to evoke a response (V2) increases above the diastolic excitability threshold (ET) by greater than 0.025 mA for a 1 msec change in coupling interval.15

During the programmed electrical stimulation protocol, premature ventricular stimuli (4 msec duration, 2x threshold) were introduced into the interventricular septum using a Grass model S-88 stimulator and a Grass model SIU-5 stimulus isolation unit. Single (S1), double (S1-S2), and then triple (S1-S2-S2) premature ventricular stimuli were introduced. Single ventricular extrastimuli were introduced during atrial pacing at S1-S2 coupling intervals decreasing from 350 msec until ventricular refractoriness occurred. Thereafter, double and triple ventricular extrastimuli were introduced during sinus rhythm at S1-S2 and S1-S2-S2 coupling intervals of 182, 167, 154, 143, 135, and 125 msec. Previous work has shown that this method fails to produce ventricular dysrhythmias in sham-operated animals without previous myocardial ischemic injury.16

Ischemia at a site remote from previous myocardial infarction: Left circumflex intimal stimulation and injury. After the completion of post treatment programmed ventricular stimulation testing, an anodal direct current of 150 µA was applied to the intimal surface of the left circumflex coronary artery via the previously inserted silver wire electrode. The lead II ECG was recorded directly onto a Grass polygraph or was recorded, at preset intervals, by a programmable cardiocassette recorder.

Upon completion of the experiment at 24 hours of electrical stimulation or upon the development of ventricular fibrillation, the heart was excised, and thrombus mass within the left circumflex coronary artery was determined after removal by careful dissection. The heart was cut into 1 cm thick transverse sections which were placed in 0.5% triphenyltetrazlium chloride in 0.01 M phosphate buffer (pH 7.4). Infarct size was quantitated gravimetrically with the aid of the differential histochemical reaction.18

Determination of serum potassium and digoxin concentrations. Blood samples for the determination of serum digoxin and potassium concentrations were obtained by venipuncture 16 hours after the preceding administration of digoxin. Serum potassium concentrations were determined by flame photometry. Serum digoxin concentrations were determined by means of radiimmunoassay technique in the Ligand Assay Laboratory of the University of Michigan Medical School, with the use of sheep antidigoxin antiserum.

Statistical analysis. For all evaluations, data are expressed as the mean ± S.E.M. Within a given treatment
Table I. Electrocardiographic and electrophysiologic responses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Digoxin (n = 13)</th>
<th>Vehicle (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>109 ± 5</td>
<td>115 ± 7</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>79 ± 4</td>
<td>79 ± 7</td>
</tr>
<tr>
<td>PR interval (msec)</td>
<td>118 ± 3</td>
<td>120 ± 4</td>
</tr>
<tr>
<td>QRS interval (msec)</td>
<td>59 ± 1</td>
<td>58 ± 2</td>
</tr>
<tr>
<td>QT, interval (msec)/sec</td>
<td>285 ± 8</td>
<td>270 ± 5</td>
</tr>
<tr>
<td>Paced QT interval (msec)</td>
<td>205 ± 7</td>
<td>189 ± 5†</td>
</tr>
<tr>
<td>Ventricular excitation threshold voltage (V)*</td>
<td>2.2 ± 0.2</td>
<td>2.5 ± 0.3</td>
</tr>
<tr>
<td>Ventricular refractory period (msec)*</td>
<td>163 ± 6</td>
<td>136 ± 6†</td>
</tr>
</tbody>
</table>

*Electrophysiologic parameters determined at the right ventricular outflow tract site during programmed ventricular stimulation.

†p < 0.05, ‡p < 0.01 before vs after within the treatment group.

Table II. Electrophysiologic responses in normal noninfarcted and infarcted zones of myocardium

<table>
<thead>
<tr>
<th>Site and parameter</th>
<th>Digoxin</th>
<th>Vehicle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>&quot;Normal zone&quot;**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitation threshold (mA)</td>
<td>0.36 ± 0.03</td>
<td>0.56 ± 0.15</td>
</tr>
<tr>
<td>Relative refractory period (msec)</td>
<td>166 ± 7</td>
<td>146 ± 3†</td>
</tr>
<tr>
<td>Effective refractory period (msec)</td>
<td>141 ± 7</td>
<td>125 ± 3†</td>
</tr>
<tr>
<td>Activation time (msec)</td>
<td>20.5 ± 1.6</td>
<td>22.6 ± 1.9</td>
</tr>
<tr>
<td>&quot;Infarct zone&quot;**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitation threshold (mA)</td>
<td>0.48 ± 0.07</td>
<td>0.90 ± 0.26</td>
</tr>
<tr>
<td>Relative refractory period (msec)</td>
<td>182 ± 9</td>
<td>135 ± 43§</td>
</tr>
<tr>
<td>Effective refractory period (msec)</td>
<td>152 ± 7</td>
<td>117 ± 5†</td>
</tr>
<tr>
<td>Activation time (msec)</td>
<td>24.2 ± 2.2</td>
<td>22.1 ± 2.3</td>
</tr>
</tbody>
</table>

*For all normal zone parameters, n = 13; infarct zone values for excitation threshold, relative and effective refractory periods are n = 9 and n = 8 for the digoxin and vehicle treatment groups, respectively. The reduction in n in the infarct zone was due to the inability to construct strength-interval curves in electrically inexcitable tissue in several animals.

†p < 0.05, ‡p < 0.01 before vs after within the treatment group and within the same zone of myocardium.
§p < 0.01 infarct zone post parameter vs paired normal zone post parameter within the same treatment group.
||p < 0.05 digoxin post treatment parameter vs analogous vehicle post treatment parameter within the same zone of myocardium.

RESULTS

Twenty-six conscious post infarction dogs were entered into the present study. These animals were randomized to treatment with digoxin (n = 13; 0.0125 mg/kg/day intravenously for a mean treatment period of 5.9 ± 0.4 days), or with vehicle (n = 13; digoxin diluent administered in matching volume for a mean treatment period of 5.3 ± 0.4 days). The pre- and post treatment responses of the post infarction dogs to electrophysiologic testing and programmed ventricular stimulation, as well as the responses of the treated animals to the subsequent development of acute posterolateral ischemia, are presented below.

Serum digoxin—Time course profile. Daily determinations of serum digoxin concentrations were performed for the first six digoxin-treated dogs completing a 7 day treatment period. Serum samples for the digoxin assay were obtained by peripheral venipuncture 16 hours after the preceding administration of digoxin. After 4 to 7 days of treatment, serum digoxin concentrations ranging from 0.80 to 2.31 ng/ml were achieved in these animals. Mean serum digoxin concentrations for treatment days 4 through 7 for this group ranged from 1.12 ± 0.30 to 1.40 ± 0.32 ng/ml (Fig. 2). All digoxin-treated dogs in this study were administered intravenous digoxin for treatment periods of 5 to 7 days before repeat programmed ventricular stimulation and electrophysiologic testing.

Programmed electrical stimulation. Twenty-six post infarction dogs were subjected to repeat pro-
Digoxin and lethal ventricular arrhythmias

Table III. Response to ischemia at a site remote from previous myocardial infarction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Digoxin (n = 10)</th>
<th>Vehicle (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to ischemia (min)</td>
<td>298 ± 33</td>
<td>219 ± 35</td>
</tr>
<tr>
<td>Increase in heart rate upon ST segment change (% of pre-ischemic rate)</td>
<td>+28 ± 7</td>
<td>+39 ± 7</td>
</tr>
<tr>
<td>Incidence of &quot;sudden&quot; ventricular fibrillation upon ischemia</td>
<td>4/10*</td>
<td>0/12</td>
</tr>
<tr>
<td>Infarct size (% of left ventricle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>6.6 ± 1.4</td>
<td>6.3 ± 1.8</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>18.3 ± 3.2</td>
<td>21.5 ± 2.3</td>
</tr>
<tr>
<td>Thrombus mass</td>
<td>12.2 ± .9</td>
<td>13.4 ± 3.2</td>
</tr>
</tbody>
</table>

*p < 0.05 digoxin vs vehicle treatment group. tIncidence of ventricular fibrillation within 60 minutes of ischemia.

Fig. 3. Mortality rates of digoxin- and vehicle-pretreated post infarction dogs after the development of posterolateral ischemia following left circumflex intimal injury.

grammed ventricular stimulation in the conscious unsedated state after digoxin (n = 13) or vehicle (n = 13) treatment. Before treatment, all dogs had been determined noninducible during programmed stimulation testing. At the time of restesting, animals in the digoxin-treated group had a mean serum digoxin concentration of 1.36 ± 0.17 ng/ml, and all dogs in both groups appeared healthy and displayed no spontaneous ventricular ectopy. Repeat programmed ventricular stimulation failed to initiate nonsustained or sustained ventricular tachycardia in 12 of 13 digoxin-treated and in 13 of 13 vehicle-treated animals. One previously noninducible digoxin-treated dog responded to repeat programmed ventricular stimulation with a rapid polymorphic ventricular tachycardia that degenerated into ventricular fibrillation, and was not resuscitated. The sizes of the underlying anterior myocardial infarctions did not vary significantly between the digoxin-treated (7.1 ± 1.4% of left ventricle) and vehicle-treated (6.3 ± 1.6% of left ventricle) animals subjected to repeat programmed stimulation.

Electrophysiologic responses. Table I summarizes the pre- and post treatment values for ECG intervals, sinus heart rate, mean arterial pressure, and for ventricular excitation threshold voltage and refractory period, determined at the right ventricular outflow tract (RVOT) site during programmed ventricular stimulation. For both treatment groups, post treatment RVOT refractory periods were significantly less than their respective pretreatment values, with the reduction in refractoriness in the digoxin treatment group being greater in magnitude than that observed in the vehicle treatment group (Table I). Digoxin administration to post infarction dogs resulted in a significant reduction in the QT interval, while ECG intervals were unaltered in the vehicle group (Table I).

Pre- and post treatment values for ventricular activation time, ET, RRP, and ERP, determined in NZs and IZs of myocardium, are presented in Table II. For both the digoxin and vehicle treatment groups, the NZ and IZ post treatment values for RRP and ERP were less than their appropriate pretreatment values. However, the reductions in relative and effective refractoriness for both noninfarcted and infarcted myocardium were consistently greater in magnitude for the digoxin treatment group than for the vehicle treatment group (Table II). The most striking electrophysiological alteration observed in this evaluation was the reduction in the RRP value for infarcted myocardium in the digoxin treatment group. After digoxin administration, the RRP value in infarcted myocardium was significantly less than the post treatment RRP value in noninfarcted myocardium within the digoxin treatment group, and additionally was significantly less than the corresponding post treatment RRP value in infarcted myocardium in the vehicle treatment group (Table II).

Response to ischemia at a site remote from previous myocardial infarction. Immediately after post treatment programmed ventricular stimulation, an anodal current of 150 μA was applied to the intimal surface of the left circumflex coronary artery in each of 10 digoxin-treated and 12 vehicle-treated post infarction dogs. At the time of this procedure, the animals in the digoxin-treated group had a mean serum digoxin concentration of 1.47 ± 0.19 ng/ml. Serum potassium concentrations of digoxin-treated
LCX INTIMAL STIMULATION (150 µA ANODAL) - 
DIGOXIN 0.0125 MG/KG/DAY

![ECG tracings showing ventricular fibrillation response](image)

**Fig. 4.** Ventricular fibrillation in a digoxin-pretreated conscious dog in response to the development of posterolateral ischemia in the presence of anterior myocardial infarction. An anodal current of 150 µA was applied to the intimal surface of the left circumflex (LCX) coronary artery at time 0. In this experiment, ECG alterations reflecting acute ischemia (widened QRS with increasing R wave amplitude, reflex tachycardia) was observed at 257 minutes of current, and were followed rapidly by the development of ventricular fibrillation. Depicted ECG is lead II.

(3.72 ± 0.09 mEq/L) and vehicle-treated (3.66 ± 0.15 mEq/L) dogs entering this phase of the evaluation were not significantly different. The responses of the two treatment groups to left circumflex intimal stimulation are summarized in Table III.

The responses of digoxin- and vehicle-pretreated dogs to posterolateral ischemia in the presence of a previous anterior infarction are compared graphically in the mortality curves depicted in Fig. 3. Within 60 minutes of the onset of ischemia, 4 of 10 digoxin-treated dogs vs 0 of 12 vehicle-treated dogs had developed ventricular fibrillation (40% digoxin vs 0% vehicle; p < 0.05). The mean time to the development of ventricular fibrillation after the onset of ischemia in these four digoxin-treated dogs was 5.3 ± 0.4 minutes, and the serum digoxin concentrations for these four animals ranged from 0.82 to 1.32 ng/ml. The incidence of arrhythmic fatalities at 24 hours after the development of posterolateral ischemia was 6 of 10 in the digoxin treatment group and 2 of 12 in the vehicle treatment group (60% digoxin vs 17% vehicle; p < 0.05), with two “late” arrhythmic deaths occurring in each of the two groups. Fig. 4 illustrates the development of ventricular fibrillation shortly after the development of posterolateral ischemia in a digoxin-treated post infarction dog.

**DISCUSSION**

*Previous clinical studies.* The use of digitalis after myocardial infarction remains controversial, due primarily to an uncertainty regarding the arrhythmogenic potential of digitalis in the setting of ischemic myocardial injury. Initial clinical investigations have not provided unequivocal evidence of an increased incidence of ventricular arrhythmias after the administration of digitalis in the post infarction period, but have been characterized largely as anecdotal, poorly designed, and/or lacking appropriate control groups, and ultimately unpersuasive. In one clinical trial involving 54 patients studied within 48 hours of admission for myocardial infarction, Lown et al. demonstrated that 48 patients (89% of total) could tolerate the single dose acute intravenous administration of 1.0 mg of acetyl strophanthidin without displaying deleterious conduction disturbances or spontaneous arrhythmias during or up to 30 minutes following drug infusion. Reicansky et al., in a randomized, double-blinded study, found no differences in the incidences of ventricular arrhythmias during monitoring periods 1 hour before and up to 3 hours after the single dose acute intravenous administration of 0.1 mg/kg digoxin (18 patients) or saline vehicle (15 patients). Recently, several large retrospective clinical studies have employed multivariate statistical techniques in an attempt to identify potential deleterious effects of chronic digitalis therapy on survival after myocardial infarction. Moss et al. and Bigger et al. have reported statistically significant associations between digitalis therapy and mortality at 4 months.
and 1 year after infarction, respectively, in patients
with left ventricular failure and ventricular arrhyth-
rias. In contrast to the preceding reports, Ryan et al.\textsuperscript{2} and Madsen et al.\textsuperscript{6} failed to detect a significant,
independent association between digitalis therapy
and post infarction mortality, although the exclu-
sion of early post infarction deaths in the former
study\textsuperscript{6} may have influenced this relationship. Bigger
and associates\textsuperscript{7} recently have extended their post
infarction patient evaluation throughout a 3-year
follow-up period, and have reported the indepen-
dent association between digitalis therapy and post
infarction mortality to be of borderline statistical
significance (0.05 < \( p < 0.10 \)). Additionally, digitalis
therapy recently has been identified as a significant
independent predictor of mortality in a patient
group consisting of resuscitated victims of cardiac
arrest.\textsuperscript{23}

\textbf{Previous experimental studies.} Experimental
studies conducted to date consistently suggest an
enhanced myocardial sensitivity to the toxic effects
of digitalis preparations during myocardial ischemia
and after myocardial infarction. Early studies dem-
onstrated a significant reduction in the intravenous
lethal threshold dosage of tincture of digitalis
infused subacutely\textsuperscript{6} or chronically\textsuperscript{8,11} after myocardial
infarction in dogs and cats. More recent investiga-
tors have demonstrated significant reductions in the
intravenous and/or intracoronary arrhythmogenic
threshold dosages of digitalis preparations (acetyl
strophanthidin or ouabain) infused during myocar-
dial ischemia,\textsuperscript{9,10} acutely after the reperfusion of an
occluded coronary artery,\textsuperscript{10} and at several days,\textsuperscript{12,13} 1
month,\textsuperscript{14} and 3 months\textsuperscript{15} after myocardial infarction
in pigs and dogs. However, the clinical relevance of
these findings has been questioned because of the
consistent use of acute rapid administrations of
clearly supratherapeutic and toxic concentrations of
the digitalis preparations in assessing myocardial
sensitivity in the setting of ischemic myocardial
injury.\textsuperscript{21}

\textbf{Present findings: The facilitation of lethal ventricular
arrhythmias by therapeutic digoxin in conscious post
infarction dogs.} In the present study, conscious dogs
in the subacute phase of myocardial infarction were
used to evaluate the proarrhythmic potential of
therapeutically-administered digoxin. The adminis-
tration of digoxin to post infarction dogs (0.0125
mg/kg/day intravenously for 5 to 7 consecutive days)
yielded trough serum digoxin concentrations of
1.36 ± 0.17 and 1.47 ± 0.19 ng/ml in animals sub-
jected to repeat programmed stimulation and left
circumflex coronary artery intimal injury, respec-
tively. These serum digoxin concentrations compare
favorably to the reported clinically therapeutic and
nontoxic range of 0.8 to 1.6 ng/ml serum digox-
in.\textsuperscript{24,26}

Digoxin-treated post infarction dogs in this study
had a significantly greater 24-hour mortality rate
after the development of ischemia at a site distant to
the area of previous myocardial infarction, as com-
pared to the vehicle-treated post infarction dogs.
This enhanced mortality was due to a significantly
enhanced vulnerability of the digoxin-treated ani-
mals toward the sudden development of ventricular
fibrillation in response to the acute ischemic epi-

dose. Programmed ventricular stimulation testing
before the development of posterolateral ischemia
failed to predict this enhanced susceptibility of
digoxin-treated post infarction dogs to the develop-
ment of ischemia-induced lethal arrhythmias, sug-
gest that the proarrhythmic actions of digitalis
may be mediated \textit{via} an alteration in the electro-
physiologic response of the infarcted heart to a new
ischemic insult, rather than solely \textit{via} an effect on
the infarcted myocardial substrate. Electrophysi-
ologic measurements conducted during this study
detected decreases in myocardial refractoriness and
excitability after both digoxin and vehicle treat-
ments, undoubtedly \textit{reflecting an evolving electro-
physiologic “healing” process after the experimental
myocardial infarction. However, the enhanced
reduction in myocardial refractoriness observed in
the digoxin group, particularly in the infarcted
myocardium, as well as the reduction in QT interval
(an ECG index for ventricular action potential dura-
tion, which in turn is a primary determinant for
cellular refractoriness), are consistent with the cellu-
lar electrophysiologic actions of digitalis. Through
an inhibition in Na+/K+-ATPase activity, digitalis is
thought to cause an elevation in intracellular calci-
um (Ca\textsuperscript{2+}in) concentration that in turn augments a
Ca\textsuperscript{2+}-dependent outward K\textsuperscript{+} conductance. This in
turn is responsible for the observed acceleration in
cardiac cell (phase 3) repolarization, a reduction in
cardiac action potential duration, and therefore
\textit{reduced cellular refractoriness}.\textsuperscript{36} Future studies will
be required to determine more fully the significance
of this enhanced reduction in myocardial refractori-
ness with regard to the increased susceptibility of
digitalis-treated post infarction dogs to ischemia-
induced ventricular arrhythmias.

\textbf{Conclusions.} In conscious dogs in the subacute
phase of anterior myocardial infarction, the admin-
istration of digoxin in a therapeutic dosage regimn
resulted in a significantly increased incidence in the
development of lethal ventricular arrhythmias in
response to ischemia at a site distant to the area of
previous myocardial infarction. This enhanced sus-
cceptibility of digoxin-treated post infarction dogs to
the development of ischemia-induced lethal arrhythmias was not predicted by programmed ventricular stimulation testing, and may involve a digoxin-mediated alteration in myocardial refractoriness, particularly in the infarcted myocardium. These experimental findings support clinical observations that digitalis therapy may constitute an independent risk factor contributing significantly to mortality after myocardial infarction.

The authors wish to express their appreciation to John Jarrett and John Larin of the University of Michigan Ligand Assay Laboratory for their assistance in the determination of serum digoxin concentrations, and to Kim Kanitz for her expert preparation of this manuscript.

REFERENCES