Overdrive suppression of conduction at the canine Purkinje-muscle junction

ROBERT F. GILMOUR, JR., PH.D., JAN R. DAVIS, B.S., AND DOUGLAS P. ZIPES, M.D.

ABSTRACT We have shown previously that overdrive suppression of conduction in depolarized His-Purkinje tissue requires conduction asymmetry. In this study we examined whether overdrive suppression of conduction can occur at the Purkinje-muscle junction, where natural asymmetry of conduction exists. Canine Purkinje-muscle preparations were superfused with hyperkalemic Tyrode’s solution (KCl 8 to 12 mM), and action potentials were recorded from Purkinje, junctional, and muscle cells. Initially, the Purkinje fiber was paced at the shortest cycle length at which 1:1 anterograde Purkinje-muscle conduction occurred. The papillary muscle then was paced for 10 to 50 beats at shorter cycle lengths during which, because of conduction asymmetry at the Purkinje-muscle junction, 1:1 retrograde muscle-Purkinje conduction also occurred. After overdrive papillary muscle pacing, Purkinje fiber pacing at the same cycle length that previously resulted in 1:1 conduction now produced transient Purkinje-muscle conduction block (overdrive suppression of conduction). The degree and duration of overdrive suppression of conduction were proportional to the rate and duration of overdrive pacing. After overdrive pacing, Purkinje cell action potential amplitude and \( V_{\text{max}} \) recovered within 300 msec, yet conduction block persisted for up to 7 sec. In contrast, excitability in papillary muscle cells near the Purkinje-muscle junction increased continuously after overdrive pacing. These data suggest that rapid activation of Purkinje cells during overdrive pacing was not required for overdrive suppression of conduction and that restoration of conduction after overdrive pacing was determined primarily by recovery of excitability in papillary muscle cells. Transient Purkinje-muscle conduction block after periods of rapid ventricular rates might account for overdrive-induced conduction disturbances normally attributed to bundle branch block.


SEVERAL CLINICAL and experimental studies have reported transient anterograde atrioventricular or bundle branch block after periods of rapid ventricular pacing.1–6 Recently the mechanism for this phenomenon, known as overdrive suppression of conduction, has been investigated in His-Purkinje tissue subjected to ischemia in vivo7 or to simulated ischemia in vitro.6 These studies suggest that rapid pacing produces a cumulative and rate-related depression of action potential amplitude and excitability in Purkinje cells that may persist transiently when the pacing rate is slowed. Asymmetry of conduction in such preparations facilitates 1:1 conduction at more rapid pacing rates during retrograde pacing than during anterograde pacing. Consequently, after a period of overdrive retrograde pacing, action potential amplitude and excitability may be reduced to such an extent that anterograde block occurs, even at slower pacing rates.

The observation that conduction asymmetry contributes to the production of overdrive suppression of conduction in depressed His-Purkinje tissue suggests that overdrive suppression may occur in other tissues under conditions that promote conduction asymmetry. Therefore we investigated whether overdrive suppression of conduction occurred at the canine Purkinje-muscle junction, since numerous studies have shown that impulse transmission across Purkinje-muscle junctions occurs more readily retrogradely than anterogradely, particularly if the junction has been exposed to agents having negative dromotropic effects.7–14 In addition, we investigated whether resumption of Purkinje-muscle conduction was associated with restora-
tion of Purkinje cell action potential amplitude and $V_{\text{max}}$ or muscle cell excitability.

**Methods**

**General.** Mongrel dogs of either sex were anesthetized with pentobarbital sodium (30 mg/kg) and their hearts were removed rapidly and placed in oxygenated Tyrode’s solution at room temperature. Purkinje-muscle preparations ($n = 29$) consisting of a free-running false tendon attached to a 2 to 3 cm crescent of papillary muscle 1 to 1.5 mm in thickness were obtained from the left ventricle and mounted in a standard tissue bath. The activation sequences of these preparations were determined to identify a Purkinje-muscle junction. For some experiments (see below), the size of the preparation was surgically reduced in three to five steps, separated by recovery periods of 30 to 60 min and repeated determinations of activation sequences, until a preparation containing the Purkinje-muscle junctional area was obtained. The dimensions of these preparations ($n = 12$) were approximately 1 to 2 mm in length and width and 1 mm in depth.

All preparations initially were superfused with oxygenated (95% $\text{O}_2$, 5% $\text{CO}_2$) Tyrode’s solution at a rate of 15 ml/min. The composition of the Tyrode’s solution (mM) was $\text{NaCl}$, 137.0; $\text{KCl}$, 4.0; $\text{CaCl}_2$, 1.8; $\text{MgCl}_2$, 0.5; $\text{NaH}_2\text{PO}_4$, 0.9; $\text{NaHCO}_3$, 18.0; $\text{KCl}$, 4.0; and glucose, 5.0. Temperature and pH were monitored continuously by indwelling probes and were maintained at 37.0 $\pm$ 0.5°C and 7.35 $\pm$ 0.05, respectively. The preparations were stimulated at a basic cycle length of 500 msec by rectangular pulses of 2 msec duration and an intensity of 1.5 times the diastolic threshold. Stimuli were delivered via bipolar platinum electrodes with an interelectrode distance of 1.0 mm. Transmembrane potentials were recorded by glass microelectrodes filled with 3M KCl (DC resistance 10 to 30 megohms). The stimulating and recording techniques have been described in detail previously.6, 14

In 12 experiments, the intracellular current threshold for excitation was determined by 10 msec duration depolarizing current pulses delivered via a standard or beveled recording microelectrode. The microelectrodes had DC resistances of 5 to 10 meghohms and were coupled to an amplifier with a rapid switching system (M707, W-P Instruments, Inc.). After delivery of the current pulse, the amplifier reverted to the recording mode and the presence or absence of an active response was determined.

**Effects of overdrive pacing on conduction at the Purkinje-muscle junction.** After an equilibration period of 60 to 120 min, the Purkinje-muscle preparations were stimulated at a cycle length of 500 msec via stimuli delivered to the false tendon. The activation sequence of the preparation was mapped by 50 to 100 microelectrode recordings, and the site of earliest activation of muscle was designated the Purkinje-muscle junction.13 Action potentials recorded from the Purkinje-muscle junction had unique action potential contours, as described previously.7-10, 14 Subsequently, a bipolar stimulating electrode was placed on an area of papillary muscle that had no overlying Purkinje cells. If such an area was not present, the preparation was discarded. The preparation was mapped again (10 to 20 recordings) to document that stimulation of the papillary muscle produced retrograde conduction from muscle to Purkinje without short-circuiting across other latent Purkinje-muscle junctions.11

To test for the presence of overdrive suppression of conduction, the false tendon was paced by a train of 50 stimuli delivered at a cycle length that was 10 to 20 msec longer than the shortest cycle length at which 1:1 anterograde Purkinje-muscle conduction occurred (250 to 450 msec). Thereafter, the papillary muscle was paced by trains of 10, 20, or 50 stimuli delivered at the shortest cycle length at which 1:1 retrograde conduction from muscle to Purkinje cells occurred (160 to 240 msec). In addition, the papillary muscle was stimulated at cycle lengths that were 10 to 100 msec longer than the shortest cycle length that produced 1:1 retrograde conduction. After overdrive pacing, the false tendon was paced at the same cycle length that, before overdrive pacing, had yielded 1:1 Purkinje-muscle conduction, and the time to the first anterogradely conducted action potential and the time to restoration of 1:1 anterograde conduction were determined.

Since overdrive suppression of conduction did not occur in any of the preparations during superfusion with normal Tyrode’s solution, the preparations were superfused with hyperkalemic Tyrode’s solution (KCl 8 to 12 mM) to reduce action potential amplitude in Purkinje cells and excitability in papillary muscle cells.14 The level of hyperkalemia was adjusted in each preparation to produce overdrive suppression of conduction without producing complete anterograde Purkinje-muscle block. Premolar studies showed that a combination of hyperkalemia, hypoxia, and acidosis produced more severe and persistent overdrive suppression of Purkinje-muscle conduction, as expected from previous studies demonstrating that a combination of hyperkalemia and hypoxia or acidosis depressed conduction more than hyperkalemia alone.14, 15 However, these preparations were not stable for long periods. Therefore we elected to study overdrive suppression of conduction with hyperkalemia alone, recognizing that higher degrees of conduction block may occur during simulated or actual myocardial ischemia.

**Effects of overdrive pacing on Purkinje cell action potentials and muscle cell excitability.** To identify potential determinants for restoration of anterograde conduction after overdrive pacing, action potential amplitude and $V_{\text{max}}$ of Purkinje cells near the Purkinje-muscle junction, action potential amplitude of junctional cells, and amplitude of foot potentials of junctional cells were determined in eight separate standard Purkinje-muscle preparations. The intracellular current thresholds ($I_{\text{th}}$) of papillary muscle cells near the Purkinje-muscle junction were determined in 12 separate shortened Purkinje-muscle preparations. Both types of preparations were superfused with normal and with hyperkalemic (KCl 8 to 12 mM) Tyrode’s solution. After trains of 10, 20, or 50 stimuli delivered at a cycle length of 200 msec, measurements were obtained at coupling intervals of 100 to 300 msec and during constant pacing at a cycle length of 300 msec.

**Statistics.** Data were analyzed by analysis of variance with repeated measures or by Student’s t test for paired data, as appropriate. Data are expressed as mean $\pm$ SEM.

**Results**

**Characteristics of overdrive suppression of Purkinje-muscle conduction.** Reproducible, stable overdrive suppression of conduction was produced in eight of 21 preparations studied; in six preparations overdrive suppression of conduction was produced but was not stable; in three preparations no suitable site for stimulation of papillary muscle was found; and in four preparations hyperkalemia either did not induce overdrive suppression of conduction or induced anterograde Purkinje-muscle conduction block at all pacing cycle lengths tested.

An example of overdrive suppression of conduction is shown in figure 1. After overdrive pacing of papillary muscle, Purkinje fiber pacing induced transient conduction block at the Purkinje-muscle junction, as evi-
Alterations of Purkinje fiber and papillary muscle action potentials and resting membrane potential during and after overdrive pacing. Changes in action potential amplitude and resting membrane potential for Purkinje cells \((n = 8)\) and papillary muscle cells \((n = 8)\) near the Purkinje-muscle junction were determined during and after overdrive pacing at the cycle length that produced maximal overdrive suppression of conduction \((160\) to \(240\) msec; train duration \(50\) stimuli). The postoverdrive pacing cycle lengths ranged from \(250\) to \(450\) msec. As shown in figure 3, action potential amplitude of Purkinje cells and papillary muscle cells decreased significantly during overdrive pacing \((\text{top panel})\). After overdrive pacing, the return of Purkinje cell and papillary muscle cell action potential amplitudes to control values was associated with restoration of \(1:1\) conduction.

Although there was no significant difference between the amplitude of Purkinje cell action potentials associated with the first conducted action potential vs those associated with restoration of \(1:1\) conduction, there was a tendency for action potential amplitude to increase slightly as anterograde pacing continued. Changes in action potential amplitude at progressively longer postoverdrive intervals, as well as the concomitant changes in \(V_{\text{max}}\), are given in more detail in figure 4. Papillary muscle cell action potential amplitudes tended to increase between the first conducted action potential and restoration of \(1:1\) conduction, but the difference was not statistically significant. Even if small changes in papillary muscle action potential amplitude did occur, they probably did not contribute to restoration of \(1:1\) conduction since, as noted previously, Purkinje-muscle conduction was all-or-none.

Resting membrane potential was reduced slightly, but significantly, during overdrive pacing in papillary muscle cells, but not in Purkinje cells \((\text{figure 3, bottom panel})\). Papillary muscle resting membrane potential returned to control values for the first conducted action potential and did not change significantly thereafter, as \(1:1\) conduction was restored.

Alterations of Purkinje fiber action potential amplitude and \(V_{\text{max}}\) after overdrive pacing. Because variations in

**FIGURE 1.** Overdrive suppression of conduction at the canine Purkinje-muscle junction. Upper and lower recordings in each panel were obtained from a Purkinje cell and a junctional cell, respectively. Papillary muscle was stimulated by trains of \(50\) stimuli delivered at cycle lengths of \(200\) msec \((A)\), \(180\) msec \((B)\), or \(160\) msec \((C)\). The Purkinje cell and junctional cell action potentials elicited by the last stimulus of the train are shown to the left. Thereafter, the Purkinje fiber was paced at a cycle length of \(400\) msec \((\text{beginning at the arrows})\). After overdrive papillary muscle pacing, Purkinje fiber pacing induced transient anterograde block. See text for discussion. Vertical calibration, \(50\) mV. Horizontal calibration, \(1\) sec. KCl = \(10\) mM.

dened by the presence of foot potentials and absence of an active response in the junctional cell recording. In all preparations, conduction across the Purkinje-muscle junction was an all-or-none phenomenon, i.e., no graded responses were seen in junctional cells and no conduction block occurred within muscle distal to the Purkinje-muscle junction. Shortening the overdrive pacing cycle length from \(200\) to \(180\) to \(160\) msec increased the time to the first anterogradely conducted action potential and the time to restoration of \(1:1\) anterograde conduction. In addition, the time to restoration of \(1:1\) conduction was increased by increasing the duration of the overdrive pacing train from \(10\) to \(20\) to \(50\) stimuli (not shown). Similar results were obtained in all eight preparations, as summarized in figure 2.
overdrive and postoverdrive pacing cycle lengths may
have obscured small changes in Purkinje cell action
potential amplitude and $V_{\text{max}}$ after overdrive pacing,
the restitution of Purkinje fiber action potential amplitu-
de and $V_{\text{max}}$ was determined after overdrive pacing
at a constant cycle length of 200 msec in eight separate
preparations during superfusion with hyperkalemic
Tyrode's solution (KCl 12 mM). Action potential
amplitude and $V_{\text{max}}$ were measured after stimulation at
coupling intervals of 100 to 300 msec and during con-
stant pacing at a cycle length of 300 msec.

As shown in figure 4, both action potential amplitude
and $V_{\text{max}}$ increased progressively as the coupling inter-
val was prolonged from 100 to 300 msec. Action poten-
tial amplitude and $V_{\text{max}}$ of the first action potential
elicited at a coupling interval of 300 msec did not differ
significantly from subsequent action potentials elicited
at the same coupling interval. However, there was a
tendency for $V_{\text{max}}$ to increase slightly (by 3 to 10 V/sec)
as the number of action potentials increased from one
to five. There were no significant differences in the
steady-state values of action potential amplitude or
$V_{\text{max}}$ for trains of 10, 20, or 50 stimuli at any coupling
interval, although $V_{\text{max}}$ tended to be lowest after a train
of 50 stimuli (table 1). The time constants for resti-
tution of action potential amplitude and $V_{\text{max}}$ also did
not differ after trains of 10, 20, or 50 stimuli (table 1).

FIGURE 3. Changes in action potential amplitude (APA) (ordinate,
top panel) and resting membrane potential (RMP) (ordinate, bottom
panel) of Purkinje cells (PF) and papillary muscle cells (PM) during
overdrive pacing (start overdrive to stop overdrive, abscissa) and during
Purkinje fiber pacing after overdrive pacing (start normal pacing, first
conducted action potential and sustained 1:1 conduction, abscissa).
Same preparations as in figure 2. *p < .05 vs value at start overdrive.
See text for discussion.

FIGURE 2. Effects of overdrive pacing cycle length (abscissa, top
panel) and train duration (abscissa, bottom panel) on the time to re-
stitution of 1:1 anterograde Purkinje-muscle conduction (ordinate, both
panels) in eight preparations. When pacing cycle length was varied, train
duration was kept constant at 50 stimuli. When train duration was varied,
pacing cycle length was kept constant at 160 to 240 msec, depending
on the preparation. Purkinje fiber pacing cycle lengths varied from 250
to 450 msec. See text for discussion.
These data corroborate the results given in figure 3 and demonstrate that restitution of action potential amplitude and $V_{\text{max}}$ in Purkinje cells essentially was complete before delivery of the first postoverdrive stimulus to the Purkinje fiber. Small increases in $V_{\text{max}}$ may have occurred as Purkinje fiber pacing proceeded, but variability within and between preparations was sufficient to prevent such changes from reaching statistical significance.

**Alterations of papillary muscle excitability after overdrive pacing.** The current threshold for all-or-none excitation ($I_{\text{th}}$) of papillary muscle was determined for coupling intervals of 200 to 4500 msec, after overdrive pacing at a constant cycle length of 200 msec in 12 separate shortened Purkinje-muscle preparations. In preliminary experiments ($n = 5$), hyperkalemia in the range of 6 to 8 mM decreased or did not affect $I_{\text{th}}$ compared with control. This result was expected from previous studies showing a reduction of $I_{\text{th}}$ in Purkinje fibers and shorter activation times across the Purkinje-muscle junction during exposure to moderate hyperkalemia. During exposure to 10 mM KCl, $I_{\text{th}}$ either did not change significantly or increased. Compared with control strength-interval curves, those during superfusion with hyperkalemic Tyrode’s solution containing 12 mM KCl ($n = 7$) were consistently shifted upward and to the right, particularly at coupling intervals of 200 to 1000 msec (figure 5, A). In addition, $I_{\text{th}}$ during control was constant for coupling intervals greater than 200 msec, whereas during hyperkalemia $I_{\text{th}}$ decreased progressively as the coupling interval was increased to 4500 msec (figure 5, A, and table 2). Values for $I_{\text{th}}$ at coupling intervals of 500, 1000, and 4500 msec did not differ after trains of 10 and 20 stimuli but were significantly increased after a train of 50 stimuli (figure 5, B).

**Alterations of junctional cell foot potential amplitude after overdrive pacing.** Stable foot potentials were recorded from Purkinje-muscle junctional cells in six of the eight preparations demonstrating reproducible overdrive suppression of conduction. Changes in the amplitudes of junctional cell foot potentials were determined after overdrive pacing and were correlated with the time to the first anterogradely conducted action potential and the time to restoration of 1:1 conduction. Although the amplitude of junctional cell foot potentials increased progressively after overdrive pacing in all preparations, the time course of changes in foot potential amplitude varied, as shown in figure 6.

Figure 6 illustrates restitution curves for junctional cell foot potential amplitude in two preparations. Restitution curves were obtained by delivering stimuli to
TABLE 1
Effects of overdrive pacing with trains of 10, 20, or 50 stimuli on postoverdrive restitution of action potential amplitude and \( V_{\text{max}} \) in canine Purkinje fibers

<table>
<thead>
<tr>
<th>Stimuli (n)</th>
<th>ssAPA (mV)</th>
<th>t-APA (msec)</th>
<th>ssV(_{\text{max}}) (V/sec)</th>
<th>t-V(_{\text{max}}) (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>82.0</td>
<td>122.1</td>
<td>100.7</td>
<td>176.8</td>
</tr>
<tr>
<td>±3.6</td>
<td>±2.8</td>
<td>±13.6</td>
<td>±6.3</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>82.2</td>
<td>118.6</td>
<td>103.1</td>
<td>187.5</td>
</tr>
<tr>
<td>±2.7</td>
<td>±2.7</td>
<td>±13.7</td>
<td>±9.1</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>81.7</td>
<td>121.4</td>
<td>96.1</td>
<td>186.8</td>
</tr>
<tr>
<td>±2.9</td>
<td>±1.7</td>
<td>±11.7</td>
<td>±11.1</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM; n = 8.

ssAPA and ssV\(_{\text{max}}\) = steady-state action potential amplitude and \( V_{\text{max}} \), respectively; t-APA and t-V\(_{\text{max}}\) = time constants for restitution of action potential amplitude and \( V_{\text{max}} \), respectively.

The Purkinje fiber at progressively longer coupling intervals after papillary muscle pacing at the cycle lengths indicated in the figure legend. In figure 6, A, restitution of foot potential amplitude was rapid and the time to the first anterogradely conducted action potential (indicated by the arrow) was short after pacing at a cycle length of 800 msec. As the pacing cycle length was shortened, restitution of foot potential amplitude slowed, although the restitution curves for cycle lengths of 350 to 600 msec differed little at coupling intervals of 200 to 300 msec.

The first conducted action potential occurred when foot potential amplitude was 12 ± 0.5 mV, regardless of the pacing cycle length. However, foot potential amplitude apparently was not the only determinant of conduction; the first conducted action potential after pacing at cycle lengths of 350 and 400 msec occurred at coupling intervals 160 to 180 msec longer than the coupling interval at which foot potential amplitude first reached its maximum value.

Restitution of foot potential amplitude usually was monotonic, as illustrated by the restitution curves in figure 6, A, after pacing at cycle lengths of 400 to 800 msec. However, the restitution curve obtained after pacing at a cycle length of 350 msec in the same preparation suggests that recovery of foot potential amplitude may have been biphasic. In two other preparations, restitution of foot potential amplitude clearly was not a simple monotonic process. An example of foot potential restitution in one of these preparations is given in figure 6, B. Note that foot potential amplitude increased exponentially at coupling intervals of 260 to 380 msec but increased sharply at coupling intervals of 390 to 400 msec and reached a maximal value at a coupling interval of approximately 450 msec. However, Purkinje-muscle conduction did not occur until the coupling interval was prolonged further to 600 msec.

Discussion

New findings. The results of this study indicate that, under conditions of hyperkalemia, transient anterograde conduction block occurred at the canine Pur-
Role of conduction asymmetry in overdrive suppression of conduction. In our previous studies in Purkinje fibers, asymmetry of conduction facilitated the production of rate-related depression of action potential amplitude by permitting retrograde pacing at more rapid rates than were possible during anterograde pacing. Under those conditions (hypoxia, acidosis, and 10 to 15 mM KCl), restoration of conduction was determined, in part, by time-dependent recovery of action potential amplitude. In the present experiments, time-dependent recovery of Purkinje cell action potential amplitude and $V_{\text{max}}$ was rapid and was independent of the duration of overdrive pacing. These observations suggest that although Purkinje cells could be paced at faster rates during retrograde than during anterograde stimulation, rate-related reduction of Purkinje cell action potentials were too transient to have contributed significantly to conduction block after overdrive pacing. More prolonged recovery of Purkinje cell action potential amplitude and $V_{\text{max}}$ would be expected under the experimental conditions used in our previous experiments, but under those conditions complete anterograde Purkinje-muscle block usually occurs.

Alterations of action potentials, excitability, and foot potentials during and after overdrive pacing. Overdrive pacing reduced action potential amplitude and $V_{\text{max}}$ in Purkinje cells and papillary muscle cells under conditions of hyperkalemia, as demonstrated previously. The mechanism for this rate-related depression of action potentials is uncertain but may relate to intracellular accumulation of sodium and extracellular accumulation of potassium.

### TABLE 2
Effects of hyperkalemia on the relationship between coupling interval (CI) and current threshold for excitation ($I_{\text{th}}$) in canine papillary muscle

<table>
<thead>
<tr>
<th>CI (msec)</th>
<th>Control</th>
<th>12 mM KCl</th>
<th>$\Delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>486.4</td>
<td>658.6$^a$</td>
<td>172.1</td>
</tr>
<tr>
<td>$\pm$ 64.6</td>
<td>$\pm$ 70.6</td>
<td>$\pm$ 26.2</td>
<td></td>
</tr>
<tr>
<td>500</td>
<td>446.4</td>
<td>588.6$^a$</td>
<td>122.1</td>
</tr>
<tr>
<td>$\pm$ 57.3</td>
<td>$\pm$ 58.8</td>
<td>$\pm$ 9.3</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>461.4</td>
<td>548.6$^a$</td>
<td>87.1</td>
</tr>
<tr>
<td>$\pm$ 57.2</td>
<td>$\pm$ 53.1</td>
<td>$\pm$ 11.1</td>
<td></td>
</tr>
<tr>
<td>4500</td>
<td>461.4</td>
<td>496.4$^b$</td>
<td>35.0</td>
</tr>
<tr>
<td>$\pm$ 57.2</td>
<td>$\pm$ 53.1</td>
<td>$\pm$ 13.9</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as mean $\pm$ SEM; n = 7.

$p < .01$ vs control; $p < .05$ vs control.

kinje-muscle junction after a period of 1:1 retrograde conduction. The degree and duration of conduction block were proportional to the rate and duration of overdrive pacing. Restoration of conduction appeared to depend primarily on recovery of junctional cell excitability, since the latter increased continuously after overdrive pacing and depended on the duration of pacing. In contrast, restitution of Purkinje cell action potential amplitude and $V_{\text{max}}$ were complete within 300 msec after the end of overdrive pacing and were independent of the duration of overdrive pacing. Restoration of conduction also was associated with restitution of junctional cell foot potential amplitude, although conduction block could be maintained in some cases despite complete recovery of foot potential amplitude.

![FIGURE 6](http://circ.ahajournals.org/). Restitution of junctional cell foot potential amplitude after overdrive pacing. A, Relationship between coupling interval (abscissa) and foot potential amplitude (ordinate) after pacing at cycle lengths of 350 to 800 msec (see legend). Arrows indicate shortest cycle length at which anterograde conduction occurred. B, Same format as panel A, but results were obtained in a different preparation. See text for discussion.
latter phenomenon may have been responsible for the small overdrive-induced depolarization in papillary muscle.\(^2\)\(^1\)

Elevating KCl concentration from 4 to 12 mM reduced papillary muscle excitability at short coupling intervals, but excitability increased as the coupling interval was prolonged. These results are similar to those reported by Rozanski et al.,\(^2\)\(^2\) who ascribed the time-dependent increase in excitability during diastole to progressively larger local responses mediated by sodium current. They observed no time-dependent changes in membrane resistance or the voltage threshold for excitation during hyperkalemia.

Our finding that the strength-interval curve was displaced upward as the duration of the overdrive pacing train was increased suggests that overdrive pacing may have produced residual depression of sodium current, despite the fact that action potential amplitude and \(V_{\text{max}}\) were not affected significantly. Alternatively, changes in excitability after longer periods of overdrive may have been caused by time-dependent reductions in sodium-potassium pump current\(^2\)\(^3\) or by changes in membrane resistance secondary to depletion of potassium that had accumulated during the overdrive.\(^2\)\(^1\)

The recovery of foot potential amplitude in junctional cells after overdrive pacing also may have been related to a time-dependent increase in the amplitude of local responses. Rozanski et al.\(^2\)\(^2\) showed that restitution of local response amplitude during diastole varied as a function of stimulus input. At “high” inputs restitution was continuous and monotonic, whereas at “lower” inputs restitution was nonmonotonic, resembling the sudden step changes in foot potential amplitude seen in the present study.

The reason for sudden changes in local response and foot potential amplitudes is not clear. Sudden changes in foot potential amplitude probably were not caused by changes in junctional cell excitability, since no abrupt deviations of \(I_n\) were seen during determination of strength-interval curves. Neither were any sudden shifts in the restitution of Purkinje cell action potential amplitude or \(V_{\text{max}}\) noted. Instead, these observations suggest that as the postoverdrive recovery interval increased, reestablishment of coupling between cells at the Purkinje-muscle junction may have occurred. In this regard, Bredikis et al.\(^2\)\(^4\) have shown that rapid pacing increases internal resistance in rabbit atrial muscle. Very rapid rates, however, may be required to produce appreciable changes in internal resistance, since Pressler\(^2\)\(^5\) found no difference in the internal resistance of quiescent sheep Purkinje fibers compared with fibers that were stimulated at a cycle length of 500 msec.

**Implications for rate-related arrhythmias.** Atioventricular conduction block and aberrancy after rapid ventricular rhythms in vivo have been attributed to conduction block within the His-Purkinje system, based on intracardiac recordings of block distal to the His bundle deflection\(^4\)\(^-\)\(^5\) and surface electrocardiographic patterns of bundle branch block.\(^2\)\(^-\)\(^3\) The results of the present study suggest an alternative possibility: that overdrive suppression of atioventricular or bundle branch conduction could be caused by conduction block at Purkinje-muscle junctions. Since conduction block at Purkinje-muscle junctions frequently is unidirectional,\(^5\)\(^-\)\(^1\)\(^3\)\(^-\)\(^1\)\(^4\) postoverdrive Purkinje-muscle conduction block could be conducive to the development of reentry.\(^2\)\(^6\)

**Limitations.** Since the passive membrane properties of cells at the Purkinje-muscle junction are unknown, it is not possible to calculate the charge required for activation of junctional cells. Consequently, it is not possible to predict from our data the action potential amplitude and \(V_{\text{max}}\) required for excitation of a junctional cell at any given time after overdrive pacing. In addition, we have only limited circumstantial evidence that changes in cell coupling (i.e., intercellular resistance) occurred after overdrive pacing. Therefore the data suggest that restoration of 1:1 Purkinje-muscle conduction after overdrive pacing depended primarily on recovery of papillary muscle excitability, but the proposed relationship between conduction and excitability cannot be described quantitatively. The contributions of small changes in \(V_{\text{max}}\) or cell coupling, if they occurred, to restoration of conduction cannot be determined.

In the present experiments, we measured the current threshold for excitability in cells near the Purkinje-muscle junction, but it was not possible to demonstrate conclusively that current thresholds were measured in the junctional cells themselves. The primary criterion by which we and others have identified junctional cells is their position in the Purkinje-muscle activation sequence.\(^7\)\(^-\)\(^1\)\(^0\)\(^-\)\(^1\)\(^4\) Once the Purkinje-muscle preparation had been reduced in size, it was not possible to stimulate Purkinje cells selectively with bipolar electrodes, nor could activation sequences be determined reliably. Therefore it is possible that overdrive pacing may have affected excitability differently in junctional cells than in the cells from which we obtained measurements.

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