Functional Dissociation of Cellular Activation as a Mechanism of Mobitz Type II Atrioventricular Block

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Background. Several mechanisms have been advanced to explain Mobitz type II atrioventricular block in the ischemically damaged His-Purkinje system. Only recently, however, has an animal model been developed to study this form of conduction defect in vivo and in vitro.

Methods and Results. Conduction defects were induced in anesthetized dogs by ischemic damage to the proximal His-Purkinje system after anterior septal artery ligation. Stable 2:1 atrioventricular block, localized within the His bundle or in the proximal bundle branches, was obtained in each dog by atrial pacing at an average rate of 239±20 beats per minute (n=12). In vitro studies were then performed from the same hearts. Action potentials and electrograms were simultaneously recorded from the His bundle and the proximal right bundle branch at the site of damage. At slow rates of pacing (40–60 beats per minute), the action potential amplitude was 85±4 mV, and some cells (10±3%) showed dissociation from the electrical activity in the bundle. At fast rates (149±11 beats per minute), during 1:1 conduction, the frequency of cellular dissociation increased to 57±6% (p<0.001), and the action potential amplitude decreased (−31±4%, p<0.001). The frequency of dissociation closely correlated with the reduction in action potential amplitude (r=0.87, p<0.001). These changes were markedly attenuated once 2:1 block developed. The site of block was not constant but rather showed a dynamic behavior with spatial shifting in response to changes in pacing rate or the introduction of extrastimuli.

Conclusions. These results indicate that in the ischemically damaged proximal His-Purkinje system, an increase in rate leads to reduced and asynchronous cellular activation before 2:1 block. The latter provides a more stable activation pattern, because the frequency of dissociation is markedly reduced.

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Key Words • arrhythmias • atrioventricular block • Mobitz type II block • heart block

The mechanism for Mobitz type II atrioventricular (A-V) block remains to be elucidated. Prolonged absolute refractory period,1 decremental conduction,2,3 supernormal conduction associated with prolonged refractoriness,4 and changes in excitability5–7 have been proposed. Not only does the mechanism remain unsettled, but its evolution over time cannot be predicted. In fact, intermittent restoration of 1:1 conduction or progression to complete A-V block often occurs unexpectedly.

We tested the hypothesis that a reduction in the number of functionally conducting fibers may be a fundamental condition for the occurrence of Mobitz type II A-V block. Under such circumstances, propagation may fail because of insufficient depolarizing current in relation to the downstream local threshold,8 i.e., loss of the safety factor. Critical to this study was the availability of an experimental preparation that shows all the characteristics of Mobitz type II A-V block, e.g., infranodal site, abrupt occurrence of A-V block, progression to complete heart block. A previously described canine model of A-V block was studied both in vivo and in vitro.9

Methods

In Vivo Studies

Experiments in this study conformed with the guidelines of the American Physiological Society. Adult mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg i.v.). After endotracheal intubation, animals were ventilated with room air by a Harvard pump. A femoral artery was cannulated to monitor blood pressure, pH, and blood gases. The left side of the thorax was opened at the fourth intercostal space. After the pericardium was opened and the left atrial appendage reflected, the anterior septal artery was identified at the level of bifurcation of the main left coronary artery. A silk ligature was passed across the artery. Occlusion was postponed until control recordings were obtained. The pericardium and the left thoracotomy were then
closed, and the dog was turned onto the left side for a right thoracotomy at the fourth intercostal space. After pericardiotomy, two pairs of plunge wire electrodes were passed through the right atrial free wall and placed in the proximal and distal His bundle areas. An electrode catheter was introduced through a carotid artery and positioned at the level of the aortic root to record the His bundle electrogram from the left side of the heart. Validation of His bundle recordings were made during His bundle pacing. ECG leads II and aVR were recorded simultaneously with the electrograms. The vagosympathetic trunk was isolated, and two Teflon-coated electrodes were introduced into the trunk for stimulation (20 Hz, 1–10 V, 0.5 msec) to transiently reduce the heart rate when required. To increase the heart rate, one pair of electrodes was secured in the high right atrium and another pair was placed in the right ventricular outflow tract for ventricular pacing.

During the control period, incremental right atrial pacing was performed until Wenckebach-type block appeared. Ventricular stimulation was performed from the right ventricular outflow tract and from the distal His bundle to obtain retrograde His bundle activation.

One-stage ligation of the anterior septal artery was performed to induce ischemic damage of the proximal His-Purkinje system. Thereafter, atrial pacing was done to exacerbate ischemia in the His bundle area. Stable conduction defects were observed 45–60 minutes after the occlusion. The atrial rate was then increased to determine the cycle length that produced 2:1 block distal to the proximal His bundle recording. The appearance of right or left bundle branch block pattern in this preparation usually indicates dissociation of conduction in the His bundle, which was confirmed by normalization of the QRS during distal His bundle pacing.

**In Vitro Studies**

A block of tissue from the same heart previously studied in vivo containing the His bundle and the proximal right bundle was exposed according to a previously described technique. The preparation was pinned to the floor of an isolated tissue bath and superfused with oxygenated (95% O₂/5% CO₂) Tyrode’s solution (36–37°C; pH, 7.35–7.45). The composition of the Tyrode’s solution was (in mmol/L): NaCl 130, KCl 4, CaCl₂ 2.7, NaHCO₃ 20, NaH₂PO₄ 0.9, MgCl₂ 1.05, d-glucose 5.5, sucrose 10. Visible, infarcted myocardial tissue was observed in the intraventricular septum underlying the proximal conducting system. The conduction tissue was stimulated through close silver bipolar electrodes insulated except at the tips. Rectangular pulses of 2-msec duration and twice diastolic threshold were used for the basic drive. Transmembrane potentials were obtained with standard glass microelectrodes filled with 3-mol/L KCl and connected to high-impedance amplifiers (WP Instruments). Stimuli were delivered to the proximal His bundle or to the proximal right bundle when conduction defects were localized in the latter. During 2:1 block, the presence of local responses recorded from the microelectrode associated with nonconducted beats was considered indicative of proximity to the site of block. Several impalements were then made within 5 mm to analyze cellular activation at different frequencies of stimulation. Since the site of block was not constant (see “Results”), no attempt was made to define the electrical activity as “proximal to,” “at,” or “distal to” the damaged area. Instead, during each impalement, the microelectrode allowed us to observe the shifts in the site of block during a given pattern of stimulation. Anterograde as well as retrograde conduction was evaluated. Dissociation, cellular dissociation, and dissociation of cellular activation, as used in the text, can be defined as impairment in the electrical coupling of a cell in relation to the activity of other cells in a bundle branch. (Also see “Discussion.”) “Partial” or “complete” dissociation of a cell from the bundle branch was considered when one or more of the following criteria were present: depolarization of a cell in the proximal portion of a bundle after the distal segment is activated; out-of-phase activation pattern (see, e.g., discussion of Figure 8); or increased stimulus-to-response ratio in the cell compared with the bundle (e.g., 2:1 activation of the cell during 1:1 activation of the distal bundle). Dissociation was evaluated during slow rates (40–60 beats per minute), during fast rates (before initiation of 2:1 block), and during 2:1 block. The frequency of cellular dissociation in a bundle was expressed as the percent of cells impaled showing partial or complete dissociation of their electrical activity. The relative magnitude of the depolarizing wave front, i.e., the ability to successfully propagate across areas of reduced conductivity, was estimated by the amplitude of the action potential in the damaged area. Modifications at fast rates were expressed as percent change from the action potential amplitude recorded at slow rates in the same cell.

Signals were displayed on a Tektronix oscilloscope, stored on tape (TEAC XR-510), and recorded (Gould TA 2000) at a paper speed of 50–200 mm/sec.

**Statistical Analysis**

Data are expressed as mean ± SEM. Student’s t test for paired data was used to assess the effects of rate and conduction pattern on cellular activation. Correlation coefficient analysis was used to compare the degree of dissociation of activation with the action potential amplitude. Differences were considered significant at p ≤ 0.05.

**Results**

**Conduction Defects Induced In Vivo**

In the control state, block could not be induced within the His bundle during rapid atrial pacing. After the induction of ischemic damage in the proximal His-Purkinje system, bundle branch block patterns frequently appeared. Two dogs showed alternating bilateral bundle branch block, and eight developed isolated right bundle branch block pattern. Infranodal 2:1 A-V block was consistently induced in each dog during atrial pacing. The average rate associated with 2:1 block was 239 ± 20 beats per minute. More advanced degrees of block and even paroxysmal complete A-V block were observed during faster atrial pacing rates.

**Mobitz Type II Block in the Isolated, Ischemically Damaged, Proximal Conduction System**

Figure 1 illustrates the in vitro preparation used in this study. Either the His bundle or the right bundle was studied. The same recording alignment as shown in Figure 1 was used in all experiments. In the ischemically
FIGURE 1. Schematic representation of the in vitro preparation of the ischemically damaged proximal conduction system. The His bundle (HB) or the right bundle (RB) was studied. Pacing was always performed from the most proximal portion of the His bundle (1) or the right bundle (4). Action potentials were obtained close to the area of 2:1 block (2,5). Electrogamms were recorded from the distal His bundle (3) or the distal right bundle (6) near the papillary muscle (PM). Retrograde stimuli were introduced close to the site where the electrogams were recorded.

damaged His-Purkinje system, 2:1 block was observed at a rate of 152±12 beats per minute. Therefore, 2:1 block in the isolated tissue occurred at a slower rate than in the anesthetized dog. Table 1 summarizes the action potential characteristics in the damaged His bundle and proximal right bundle in 12 preparations.

Figure 2 shows intracellular and extracellular record-ings obtained in the right bundle before and during 2:1 block. The bundle was paced at its origin from the His bundle, and the intracellular activity was recorded about 10 mm distally, close to the area of block. The electrogamms were obtained just proximal to the ante-rior papillary muscle and identified those impulses that successfully propagated to the end of the bundle. When the cycle length was decreased from 800 to 500 msec, 1:1 conduction was maintained, and as expected, the action potential duration shortened (−23%). The action potential amplitude decreased (−8%), with no change in the level of the resting potential (see lower dashed line). When the cycle length was shortened to 400 msec (lower panel), 2:1 block developed close to the microelectrode, since brief action potentials associated with nonpropagated beats were recorded.16-18 These brief action potentials showed cyclical changes in their amplitude consistent with varying degrees of penetra-tion in the damaged tissue.16-18 The brief action poten-tials with the lowest amplitude originated from a more positive take-off potential.21

Reduction in Action Potential Amplitude Preceding the Initiation of 2:1 Block

Under conditions of depressed conduction, a reduced action potential amplitude decreases the electrotonic source current available for propagation and may result in conduction block.6,19,20 The baseline values for action potential amplitude at a slow rate of pacing are presented in Table 1. During pacing, a rate-related decrease in action potential amplitude became manifest. Figure 3 is a continuous recording from an ischemically damaged His bundle and shows the course of the action potential amplitude, recorded at the site of block, at progressively faster rates. A decrease in cycle length from 490 to 340 msec (upper panel) resulted in a progressive decrease in action potential amplitude (−38%, as emphasized by the dashed lines) before 2:1 block in the distal bundle appeared (lower panel). Concurrently, the electrogram recorded from the distal His bundle also decreased in amplitude (−49%), suggesting a similar phenomenon in other fibers. The decrease in action potential amplitude was not secondary to a change in the take-off potential, since it remained stable, as emphasized by the dashed line under the action potentials. Once 2:1 block appeared, the action potential amplitude returned to baseline levels (last two action potentials in the lower panel). Transition to 2:1 block was preceded by marked reduction of the electrogram in every other beat (lower panel, upward arrows). Action potentials were still recorded, consistent with failure of propagation between the intracellular and extracellular recording sites. Thereafter, these small electrograms and the corresponding action potentials disappeared simultaneously, indicating proximal displacement of the site of 2:1 block (see small diagrams at the bottom of the figure). The absence of brief action potentials during nonconducted beats indicates that the site of block was relatively far from the microelectrode. Figure 4 summarizes the change in action potential amplitude as a function of rate and conduction pattern in 10 preparations. The decrease in action potential amplitude at fast rates (149±11 beats

**TABLE 1. Action Potential Characteristics in the Ischemically Damaged Cells of the Proximal Intraventricular Conducting System**

<table>
<thead>
<tr>
<th>Resting potential (mV)</th>
<th>AP amplitude (mV)</th>
<th>AP duration (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−73.1±2.4</td>
<td>84.9±4.2</td>
<td>336.3±23.9</td>
</tr>
</tbody>
</table>

AP, action potential. AP duration was measured at 90% repolarization. Values were obtained at a cycle length of 1,000–1,500 msec and expressed as mean±SEM.
per minute) averaged $-31.2\pm4.3\%$ compared with slow rates ($p<0.001$). This decrease was attenuated once 2:1 block occurred ($-5.0\pm1.5\%$, NS).

**Transition from 2:1 to 1:1 Conduction Pattern**

The changes that precede resumption of 1:1 conduction from 2:1 block can be observed in Figure 5. Pacing at the proximal His bundle with cycle length of 370 msec resulted in 2:1 conduction to the distal His bundle (upper panel, electrogram). The intracellular recordings were obtained in the middle portion of the His bundle. During stable 2:1 conduction pattern (first three beats), each propagated action potential was followed by a brief action potential (arrows) that did not activate the distal bundle, since no electrogram was recorded. Progressive prolongation of the pacing cycle length to 450 msec resulted in gradual increase in the amplitude of the nonpropagated brief action potentials until 1:1 conduction in the peripheral His bundle was obtained. The last beat in the upper panel marked the transition from 2:1 to 1:1 and showed a latency between the brief and full action potentials. This delay probably indicates that the depolarizing wave front barely succeeded in overcoming an area of poor conductivity.\(^6^7\) The following beats (lower panel) resulting in 1:1 conduction showed a notch in the upstroke of the action potential also consistent with the presence of a depressed area of conduction. Transient 2:1 conduction

**FIGURE 3.** Tracings showing reduction in action potential amplitude during proximal His bundle (HB) pacing at progressively faster rates (continuous tracing). The cycle length was reduced from 490 to 340 msec. Stable 2:1 block followed a sudden reduction in the amplitude of every other electrogram (upward arrows). The small diagrams below the recordings indicate the presence or absence of 2:1 block and the estimated location in the bundle in relation to the microelectrode impalement site.

**FIGURE 4.** Bar graph showing percent reduction in action potential amplitude (APA) compared with slow rates (40–60 beats per minute) according to rate and conduction pattern (10 preparations). Reduction at fast rates before 2:1 block ensues (RAPID, 1:1 COND) and during 2:1 conduction (2:1 COND).

**FIGURE 5.** Tracings showing increase in the amplitude of brief action potentials before resumption of 1:1 conduction in the His bundle (HB). Increase in the pacing cycle length from 370 to 450 msec. One-to-one conduction is observed in the last two beats in the upper panel and in the lower panel, transiently interrupted by two cycles of 2:1 block. The first beat that marked the transition between 2:1 and 1:1 (last beat, upper panel) showed a latency between the brief action potential and the full action potential. Diagrams are similar to those in Figure 3.
(lower panel) was associated with decrease in the amplitude of the brief action potentials. The action potential duration and the level of the take-off potential were not constant and appeared to influence the amplitude of the local responses. That is, the more negative the membrane potential at the time of activation, the larger the amplitude of the brief action potential.\textsuperscript{21}

**Displacement of the Site of 2:1 Block**

Rapid shifts in the site of 2:1 block were observed spontaneously or after the introduction of a retrograde stimulus. Figure 6 illustrates this phenomenon in an ischemically damaged preparation of the right bundle. Two-to-one block occurred proximal to the microelectrode recording site, since no local responses were seen (see small diagram in the left upper corner of the figure). After a distal stimulus was introduced (upward arrow), 1:1 conduction was maintained for four beats. An action potential preceded each electrogram, indicating participation of the cell in the propagating wave front. Note the increased latency of the electrogram in response to the preceding stimulus and the reduced amplitude of both action potentials and electrograms, consistent with a decreased depolarizing wave front penetrating the bundle. The cell responded 1:1 but with a reduced take-off potential (dashed line). The next several impulses reached the cell impaled, but every other impulse failed to propagate to the distal bundle. Therefore, 2:1 block occurred between the cell impaled and the distal electrogram (diagram at the right upper corner). The electrogram recovered the previous amplitude once 2:1 block returned. Cyclical variations in the amplitude of the nonconducted action potentials appeared (open arrowheads). Eventually, these action potentials gradually decreased in amplitude until they disappeared, indicating that the site of block gradually returned to its original location, i.e., proximal to the intracellular recording site (left, middle, and right lower diagrams).

**Disassociation in the Damaged Bundle**

Disassociation of the electrical activity of a cell from the rest of the bundle was a commonly observed response to increase in the ischemically damaged preparations. Figure 7 depicts the phenomenon of cellular dissociation in an ischemically damaged His bundle. The top panel shows simultaneous action potentials and distal electrograms during proximal His bundle stimulation at a cycle length of 1,200 msec. The stimulus–response latency for the cell was 130 msec and for the double potential electrogram was 70 msec. That is, the proximal cell was depolarized only after the impulse reached the more peripheral bundle. The dashed lines emphasize the delayed activation of the cell in relation to the distal electrogram. The lower panel shows the response of the same preparation to rapid pacing. A decrease in the pacing cycle length from 700 to 400 msec resulted in an increase in the stimulus–response latency followed by temporary loss of cellular activation for seven consecutive beats. However, 1:1 activation of the distal bundle remained unaltered. Eventually, 2:1 block developed both in the cell and in the distal bundle. The first action...
potential preceded the electrogram (possible transient involvement in the depolarizing process), but thereafter the cell was activated later than the distal bundle. Therefore, the cell did not participate in the depolarizing process at slow rates of stimulation, and its degree of dissociation increased even further during rapid pacing. Another feature of dissociation is shown in Figure 8. The proximal ischemically damaged right bundle was paced at progressively faster rates. Decreasing the cycle length from 270 to 230 msec resulted in gradual decrease in the action potential amplitude (−15%) until 2:1 block developed. Typically, the action potential amplitude recovered once 2:1 block appeared. As expected, conducted beats were associated with action potentials and nonconducted beats with local responses.

After a retrograde stimulus was introduced from the distal right bundle, however, the 2:1 periodicity in the cell was reset. Thereafter, the action potentials were associated with nonconducted beats and the local responses with conducted beats. Therefore, the cell remained dissociated from the conduction process, being activated by the nonconducted beats.

Four additional experiments were performed to investigate the presence of dissociation between cells in the ischemically damaged bundle. Intracellular recordings were obtained simultaneously from two or three cells located close together along with an extracellular recording in the distal bundle. Figure 9 shows intracellular recordings in the damaged area of the right bundle obtained from two cells located 1 mm apart (see small diagram). In each panel, the upper and the lower intracellular recordings correspond to the more proximal and the more distal cells, respectively. The tracing at the bottom is the electrogram. In panel A, the proximal right bundle was paced at a cycle length of 320 msec, and 1:1 activation occurred at the three recording sites. In panel B, 1:1 activation persisted at a cycle length of 250 msec, and as expected, the action potential duration shortened in both cells. The amplitude of the more proximal cell decreased markedly (−31%), but it remained stable in the other cell. When the cycle length was shortened to 240 msec (panel C), 1:1 activation persisted in the more proximal cell and in the distal right bundle. The cell located between these two sites, however, showed a 2:1 activation pattern and therefore became dissociated from the more proximal cell as well as from the more distal portion of the bundle. The action potential duration increased, consistent with reduction in the effective activation rate. Each fully developed action potential was followed by a small response of varying amplitude. Further decrease in the cycle length (panel D) was associated with stable 2:1 block in the three recording sites. The amplitude of the more proximal cell returned close to baseline values (23%). Therefore, reduction in action potential amplitude and functional cellular dissociation can occur simultaneously in cells located close together preceding the development of 2:1 block. Cell-to-cell dissociation was observed in all four preparations studied when the rate was increased.

Figure 10 depicts the frequency of dissociation in 10 preparations. In each preparation, an average of 20±2 cells were impaled within the damaged area. The response was evaluated as a function of the stimulation rate and the conduction pattern, as judged from the peripheral electrogram. At a slow rate of pacing (40-60 beats per minute), 10.5±3.1% of the fibers impaled showed dissociation in activation. The degree of dissociation increased markedly during rapid pacing to 56.5±6.1% (p<0.001) at an average rate 149±11 beats per minute, just below the one that resulted in 2:1 block. The degree of dissociation decreased after 2:1 block occurred (8.9±2.8%), accounting for a more stable pattern of conduction.

Relation Between the Percent of Dissociated Cells and the Action Potential Amplitude

We hypothesized that, under conditions of reduced conductivity, dissociation of cellular activation should decrease the depolarizing current (and the action po-
tential amplitude), which in turn should facilitate the appearance of dissociation.

We compared the degree of dissociation with the action potential amplitude at fast rates of stimulation before and after 2:1 block developed. Figure 11 shows a positive trend between both variables \( r=0.87, a=5.84, b=1.48, p<0.001 \), indicating that the magnitude of action potential amplitude reduction was proportional to the degree of dissociation in cellular activation in the damaged bundles.

**Discussion**

The two major findings of this study are the rate-dependent appearance of cellular dissociation and the dynamic behavior of the site of block in the ischemically damaged conduction system.

In 1913, Mines\(^2^2\) showed that during rapid pacing of the frog ventricle, two apparently different states of equilibrium could exist, a whole or a half rhythm, i.e., 1:1 or 2:1 stimulus/response. He described these equilibria as "metastable conditions" because during either state, a properly timed extrastimulus could induce a transition from one form to the other. He also noted that "the transition ... is marked by a period of

**Figure 9.** Tracings showing rate-dependent, functional dissociation of a cell from another cell and from the distal right bundle (RB). Two closely located cells were impaled simultaneously in the damaged area (see small diagram in center of figure). The more distal cell (middle tracing in each panel) became dissociated at a cycle length of 240 msec (panel C), whereas 1:1 activation persisted in the more proximal cell (upper tracing) and in the distal bundle (lower tracing). Shortly thereafter, a stable 2:1 activation pattern developed in the three recording sites (panel D). PM, papillary muscle.

**Figure 10.** Bar graph showing percent of dissociated cells as a function of rate and pattern of conduction in 10 preparations. Dissociation of activation was maximal at fast rates before 2:1 block developed (RAPID, 1:1 COND). In contrast, dissociation decreased at slow rates (SLOW, 1:1 COND) and during 2:1 block (2:1 COND).

**Figure 11.** Scatterplot showing correlation between the frequency of cellular dissociation and the action potential amplitude before \( n=10 \) and after \( n=10 \) 2:1 block developed. A positive significant trend was observed between the two variables \( p<0.001 \).
alternation . . . [or] . . . a period of partial tetanus” in the mechanical activity.

In the present experiments, the same equilibria and metastable states described by Mines were observed by simultaneously monitoring cellular electrical activity close to the site of block and electrograms distally. Thus, in Figures 3 and 6–8, discordant stimulus/activation ratios are seen in the cell and the electrogram before a more stable conduction pattern is attained.

The results of this study demonstrate that dissociation of cellular activation is a frequent phenomenon in the ischemically damaged His-Purkinje system. The extent of cellular dissociation increases markedly at fast rates of stimulation. This means that as the rate is accelerated, an increasing number of fibers “drop out” of the activation process. Probably secondary to progressive dissociation, the amplitude of the action potential decreases, reducing the ability of impulses to propagate across areas with impaired or reduced intercellular connections. Conversely, it is quite possible that a reduced action potential amplitude favors the appearance of dissociation. Eventually, 2:1 block develops, providing a more stable conduction pattern by decreasing the degree of dissociation.

In contrast to experiments with normal Purkinje fibers subjected to an abnormal extracellular milieu, the site of block was not fixed in the present preparation of the damaged conduction system. Displacements of the site of block along the bundle were frequently observed, suggesting a variable number of fibers recruited in the activation process. Improvement and deterioration of conduction were preceded by distal and proximal shift of the site of block, respectively.

Mechanism of Mobitz Type II A-V Block

The electrophysiological basis for Mobitz type II A-V block is still uncertain. Clinical studies have indicated that the PR interval before and after a blocked beat remains constant or shows a small prolongation. In addition, block usually occurs unexpectedly, since there are no indicators of impending conduction failure. Based on these observations, it has been proposed that a prolonged absolute refractory period with a shorter than normal relative refractory period explains the abrupt change from conduction to block and vice versa. Obtaining His bundle recordings at high speed, El-Sherif et al. demonstrated the existence of supernormal conduction in the presence of a prolonged refractory period during 3:2 periodicities.

Traditionally, block in a conduction bundle upon reaching a critical cycle length has been interpreted as limited by a prolonged refractory period that may outlast the action potential duration. Our data, however, suggest that the refractory period in a damaged bundle can be determined not only by the reaction time of depolarizing inward currents but also by the number of fibers available for activation. Indeed, there is now evidence indicating that under conditions of depressed conduction, the amplitude and homogeneity of the depolarizing current can modulate the ionic responses in the distal tissue. Therefore, the amplitude and rate of rise of the action potentials are determined not only by the inward current in individual cells but also by the characteristics of the excitatory current. The reduction in action potential amplitude and the appearance of dissociation, as demonstrated in the present experiments, strongly suggest that the excitatory wave front is reduced in the ischemically damaged conduction system, reducing in turn the depolarizing currents in the downstream cells.

Dissociation of Cellular Activation

Dissociated ischemic cells do not actively participate in the conduction process and therefore resemble the so-called “dead-end pathway cells” that normally exist in the A-V node. Interestingly, the A-V node shows dissociation of conduction and a low safety factor for conduction because of the low level of the resting potential and an increased intercellular resistance. These factors correspond with the rate-dependent changes in conduction and refractoriness in the A-V node and its propensity for block.

Both extracellular and intracellular resistance are increased in the ischemic myocardium, but the effect of ischemia on the intraventricular conduction system has not been established. Our results show that, at fast rates, propagation of the depolarizing wave front is markedly impaired in the ischemically damaged bundles as a result of functional dissociation of cellular activation. Our results are in agreement with recent observations made in subendocardium of infarcted papillary muscle, where, at fast rates of pacing, the electric response becomes asynchronous in different groups of cells.

Experiments in isolated cells are also consistent with the role of cellular dissociation in the development of conduction block. In fact, Tan and Joyner demonstrated that the intercellular resistance determines the ability of an isolated ventricular cell to respond to rapid pacing and that the same pacing rate may result in 1:1 or 2:1 conduction, depending on the cell-to-cell coupling resistance. Thus, the finding of cells responding in a 2:1 pattern during 1:1 conduction in the bundle is consistent with an increased intercellular resistance that prevents the normal accommodation of the refractory period to a change in rate.

Changes in Action Potential Amplitude

The present experiments show that in the damaged bundles, the action potential amplitude decreases at fast rates even though the resting potential remains stable. This observation suggests that a mechanism not related to voltage-dependent inactivation of the sodium channel may be operating. In fact, similar observations have been made in well-polarized fibers proximal to a site of block. The decrease in action potential amplitude can be independent of dV/dt changes. Accumulation of extracellular potassium and intracellular sodium and calcium and incomplete recovery of the slow channel have been proposed to account for this response. Regardless of the mechanism, in the presence of marginal conduction, the decrease in action potential amplitude results in reduced electrotonic input (source current) to the distal segments that may lead to block.
Action Potential Amplitude and Cellular Dissociation

Under ischemic conditions, cell-to-cell uncoupling develops after 15–20 minutes, probably secondary to increase in \([\text{Ca}^{2+}]\), and \([\text{H}^+]\). According to the local circuit current concept, the propagation of the electrical impulse depends on the inward depolarizing current, the intracellular and extracellular longitudinal resistances, and the membrane capacitance. An increase in intracellular resistance decreases the ability to transfer electrotonic responses from cell to cell and therefore the ability to induce an action potential. The amplitude of the action potential determines the magnitude of the electrotonic potential across an excitable area. Therefore, conduction can be critically dependent on the amplitude of the action potential under conditions of marked cellular dissociation, as in the ischemically damaged His-Purkinje system.

Study Limitations

Dissociation of cellular activation is probably a manifestation of decreased cell-to-cell coupling as well as altered membrane properties induced by ischemic damage. Although evidence supporting both abnormalities has been obtained in the present experiments, intracellular resistance and transfer of action potentials between adjacent cells were not determined. Studies in isolated cells obtained from the ischemically damaged conduction system may provide additional information on cell-to-cell interactions under abnormal conditions. It is possible that more simultaneous impalpements in the small damaged area, such as those obtained with microelectrode brushes, may improve the quantification of cellular dissociation. However, the addition of mechanical damage may limit its application.

In the human heart, block in the conduction system sometimes occurs when the rate is decreased. This phenomenon was not investigated in the present study.

Potential Clinical Significance

In several of the present experiments, changes in the action potential preceding the onset of 2:1 block corresponded with parallel modifications in the electrogram. Similar findings might be observed in the electrograms recorded from the human conduction system during pacing. These changes might be used to identify a reduced safety factor for conduction before heart block develops.

Experimentally, we have found that once Mobitz type II A-V block has developed, a retrograde stimulus can distally displace the site of block or even improve conduction. Early activation of the area of block and changes in excitability have been observed to result in improvement of conduction. This observation can lead to the development of pacing strategies designed to restore conduction in patients with heart block.

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References

5. Hay J: Bradycardia and cardiac arrhythmias produced by depression of certain of the functions of the heart. Lancet 1906;1:139–143
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M D Gonzalez, B J Scherlag, P Mabo and R Lazzara

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