Conduction through a Narrow Isthmus in Isolated Canine Atrial Tissue

A Model of the W-P-W Syndrome

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SUMMARY
Isolated blocks of dog atrial tissue were dissected to provide a narrow isthmus connecting two broader areas. Unidirectional block was readily demonstrable at the junctions of the narrow band with the larger areas. Transmembrane action potentials just proximal to the blocked junction were abbreviated, while only local electronic potentials were recorded beyond. Acetylcholine restored 1:1 propagation in blocked preparations. The model may explain some of the features of intermittent preexcitation.

Additional Indexing Words:
Acetylcholine and atrial conduction Conduction block Preexcitation syndrome

It is widely believed that the preexcitation pattern of the Wolff-Parkinson-White (W-P-W) syndrome is due to an aberrant A-V connection that conducts more rapidly than the A-V node. The conduction anomaly is often intermittent, and is sometimes exposed only in the presence of enhanced vagal activity. It has been stated that anomalous conduction occurs only when conduction through the A-V node is depressed, but intermittently accelerated A-V conduction over aberrant communications is obviously not the result of depression of the normal pathway; it is the result of enhancement of conduction over the abnormal route.

If such abnormal routes exist, they could be small strands of muscular tissue, or modified muscular tissue, which form a narrow isthmus connecting a broad sheet of atrial myocardium with a three-dimensional mass of ventricular muscle. If this is true, then the geometry of the insertion of such a narrow band into the larger mass would provide a junction in which the margin of safety for successful propagation is low. In other words, there may be an "impedance mismatch" between them. The isthmus may conduct an impulse quite effectively throughout its entire length, but at the point where it inserts abruptly into a profusely interconnected, three-dimensional mass of ventricular myocardium its limited wave front might be insufficient to bring the larger volume of cells to threshold. In accord with recent observations by Mendez and his associates, low-resistance communications between cells would, in effect, drain off or dilute the relatively small input current from the isthmus. The success or failure of propagation at the junction would then depend on the efficacy of the wave front, which in turn would depend on the amplitude and rate of rise of the action potential of the isthmus and on the excitability and connectivity of the tissue at the junction.

If these concepts are valid, it should be possible to construct a model in which the geometry is artificially modified to provide...
junctions with a low margin of safety. This we have attempted to do in atrial tissue.

**Methods**

Blocks of tissue were excised from the ventral surface of the right atrial appendage of anesthetized dogs (pentobarbital, 30 mg/kg) and pinned to the floor of a perfusion chamber irrigated with modified Tyrode's solution at a temperature of 37°C. A narrow isthmus of tissue, communicating between two larger areas, was created by sharp dissection, as schematically shown in figure 1. The incisions were placed to provide abrupt junctions between the ends of the isthmus, x and y, and the corresponding larger areas, X and Y. The dimensions of the isthmus were critical; in successful preparations the isthmus was about 5 mm long, and from 0.5 to 1.0 mm wide. The dimensions of the functionally intact fibers within the isthmus were, of course, not known. After time was allowed for "healing" of the cut surfaces, bipolar stimulating (S) and recording (R) electrodes were placed on each side of the isthmus, and microelectrodes were inserted into cells at each end of the isthmus, at the sites where the margin of safety for conduction was expected to be low.

In most experiments, the potassium concentration of the perfusion fluid was 5.4 mEq/liter; in one experiment block was induced by elevation of [K] to 8.0 mEq (figs. 2 and 3).

**Results**

If the hypothesis is correct, and if the preparation were perfectly symmetrical, then a response induced in X might be expected to block at the junction of the isthmus with Y, whereas a response initiated in Y should be blocked at the opposite junction. Although complete symmetry was not achieved, the junctional areas were regularly shown to be the sites of unidirectional block; and the block was in the direction x → X, or y → Y, not the reverse.

As has been shown in A-V-nodal transmission and at Purkinje-papillary muscle junctions, conduction failure was invariably accompanied by abbreviation of the action potentials recorded just proximal to the site of block. In the experiment illustrated in figure 2, the preparation was driven at a cycle length of 1000 msec by stimuli applied to area X (fig. 1). The bottom trace in each panel represents the electrogram recorded from X near the stimulated site. The lower transmembrane action potential was recorded at x, the upper one at y, and the uppermost trace is the electrogram recorded beyond the isthmus in Y. In Part A of figure 2, each response was propagated from X to Y; in part B, conduction failure was induced by elevation of the potassium concentration. The action potential recorded at y was greatly abbreviated, and no response was recorded in Y. Superimposed projections of the propagated
MODEL OF THE W-P-W SYNDROME

Abbreviation of action potentials near site of block: tracings, from above; extracellular electrogram from Y; transmembrane action potentials from y and x; electrogram from x. Driving stimuli applied to X. (A) Propagation proceeds from X to Y. In the upper trace, the first "pip" is the shock artifact; the second is the response. Between A and B, elevation of [K] to 8 mm. (B) Block occurs between y and Y. The abbreviation of the action potential at y is indicated by the superimposed tracings at the right. Scales at right in A, and in subsequent figures, 100 mv and 100 msec.

and blocked action potentials are indicated at the right. That the difference in the action potentials was the result of conduction failure, and not of the increased \([K^+]_o\) per se, is evidenced by the lack of any significant difference in the action potentials recorded at x.

The experiment of figure 2 suggests that conduction failure occurred just beyond the cell impaled at y, but it does not prove that failure resulted from the abrupt change in the dimensions of the conduction pathway. It was possible, of course, that the tissue at y was more severely damaged by the dissection. Figure 3, taken from the same experiment, indicates that the block was unidirectional. The first two responses were evoked by stimuli applied at Y; the other two responses were initiated, as in figure 2, at X. Propagation was

Unidirectional block at the junction yY. Same preparation and same conventions as in figure 2. The first two responses, initiated at Y, are propagated to X; the second two, initiated at X, are blocked between y and Y.
Unidirectional block at junction Y. (A) The two traces were recorded just proximal (lower trace) and distal to a site of block at Y; stimuli applied to X. (B) Stimuli applied to Y; no block occurs.

successful from Y to X, but not in the reverse direction.

If the abbreviated action potentials recorded at Y in figure 2B and at the right of figure 3 are truly representative of block, then intracellular records just beyond the site should show no more than local responses. This is apparent in figure 4A, recorded in another experiment. The micro electrode responses were recorded just proximal and distal to a site of 2:1 block at a distal junction. Excitation in the reverse direction, and at the same frequency, engaged both cells (fig. 4B).

We have suggested that propagation of an impulse at the junction between an isthmus and a larger mass of tissue will depend upon the amplitude and rate of rise of the action potentials at the distal end of the isthmus and upon the threshold of the distal mass of interconnected cells. Thus, any agent that improves the action potentials and therefore, increase the margin of safety for transmission at the critical junction. That this does occur is shown in figure 5.

Records were obtained (from top to bottom) from the proximal mass (Y), proximal junction, distal junction, and distal body. When the area Y was stimulated at a basic cycle length of 380 msec, 2:1 block occurred at the distal junction as shown in A. Abbreviated action potentials at the distal junction characterized the blocked responses. Between A and B, acetylcholine was added to the perfusion fluid in a concentration of $5 \times 10^{-7}$ g/ml. In B, every response was propagated. The improvement in the action potentials at the distal junction is obvious. In the presence of acetylcholine, one-to-one propagation across the formerly blocked junction was now possible at considerably more-rapid driving rates; 1:1 propagation was now maintained at a cycle length of 130 msec (fig. 5C).

Discussion

In detailed studies of the characteristics of propagation in partially refractory tissue, Mendez and his collaborators have empha-
sized the effect of low resistance intercellular connections upon action-potential duration and configuration.3,4 Electrotonic interactions between active elements proximal to a site of block and inactive elements beyond the junction can remarkably accelerate the repolarization of the proximal cells. In more recent studies they have demonstrated the importance of the geometry of intercellular connections as exemplified by the junctions between terminal Purkinje fibers and the ventricular muscle cells that they serve.5 Under normal conditions the attenuated cable represented by the terminal Purkinje fiber supplies an adequate source of electrochemical energy to bring the divergent syncytial mass of muscle cells to their excitation threshold, but when the action-potential amplitude of the Purkinje fiber is reduced, or the excitability of the muscle it supplies is diminished, as with early premature excitation, the margin of safety for propagation may fall below one. That the geometry of the junctions becomes crucially important is illustrated by the persistence of effective transmission from muscle to Purkinje fiber under conditions that do not allow conduction in the normal direction.

The model described in the present study behaves in many respects like the Purkinje-muscle junction. Unidirectional block can be readily demonstrated where a narrow strand inserts abruptly into a larger mass of tissue, while conduction from the larger mass to the isthmus persists. As in the Purkinje-muscle junction, action potentials recorded proximal to the blocked site are conspicuously abbreviated. While it might be argued that conduction fails because the action potentials have "decremented," it is probably more accurate to

**Figure 5**

*Block relieved by acetylcholine. For description see text.*
state that the action potentials are attenuated and abbreviated because block occurred.

The characteristics of transmission in the model permit some reasonable conjectures about the behavior of aberrant A-V communications. If these are narrow strands of atrial muscle that insert abruptly into the three-dimensional ventricular syncytium, the margin of safety at the junction may be expected to be low. If it is critically poised near the value of 1.0, small changes in membrane potential, membrane “responsiveness,” or excitability could spell the difference between preexcitation and normal A-V delay. If the strands are, like ordinary atrial muscle, exposed to and responsive to acetylcholine liberated by vagal excitation, then the W-P-W pattern would be elicited by increased cholinergic discharge. A moderate increase in extracellular potassium concentration (which enhances conductivity in both atrial and ventricular tissue) could bring out the preexcitation pattern, while more extreme hyperkalemia could suppress it.

Depending upon the geometry of an aberrant connection, conduction might regularly fail in the A-V direction and regularly succeed in the V-A direction. In other words, it could be possible to have the anatomic substrate for the W-P-W syndrome, including the possibility of paroxysmal supraventricular tachycardia or atrial fibrillation, without ever demonstrating anomalous A-V conduction.

Consider, for example, the sequence of excitation that must occur if conduction always fails at the junction between an aberrant bundle and the ventricular myocardium. The ventricular muscle at the junction will be excited over the normal route through the A-V node and the His-Purkinje system, but it will be excited at a time when the atria are still refractory. There will be no retrograde P wave and no other discernible evidence of an aberrant connection. Suppose now that the P-R interval is prolonged by increased vagal activity, and that the atrial refractory period is abbreviated by the same cholinergic agency. The conduction time to the site of the junction may now exceed the refractory period of the atrium, and reexcitation may occur. Depending upon the timing of events, this could take the form of a single retrograde P wave (an atrial “echo”), a paroxysm of reciprocal rhythm, an episode of atrial flutter, or the initiation of atrial fibrillation.

Because otherwise unexplained episodes of tachyarrhythmias may in fact be due to aberrant connections that never propagate in the A-V direction and are therefore never exposed by routine electrocardiographic examination, it is perhaps worth considering how the diagnosis might be accomplished. The induction of atrial premature beats by means of a transvenous stimulating electrode could result in atrial echoes, but this could be the result of intranodal dissociation and is probably demonstrable in most normal hearts. Reflexly induced vagal activity by itself should not generate atrial echoes in the normal heart, but if the P-R interval were sufficiently prolonged, retrograde P waves might occur if an aberrant pathway were present. If, however, the heart rate is sufficiently depressed, the frequency-dependent changes in atrial refractory period and in A-V conduction could prevent the exposure of retrograde atrial responses. A combination of vagal stimulation with atrial pacing (to prevent bradycardia) might well provide the necessary conditions. Finally, reflexly induced bradycardia, coupled with induced ventricular premature beats, might expose a functional V-A communication. Retrograde conduction through the A-V node in this situation should be prolonged, but propagation over an extranodal pathway should result in a retrograde P wave closely coupled to the QRS complex.

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