Unmasking of Ventricular Preexcitation by Vagal Stimulation or Isoproterenol Administration

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SUMMARY Twenty-one patients were studied in whom ventricular preexcitation (VP) had been recorded in the past and had later disappeared, indicating antegrade block in the accessory pathway (AP), either spontaneously (10 patients) or under the effect of chronic treatment with amiodarone (11 patients). VP reappeared in nine cases during vagal stimulation, and in five cases during an i.v. isoproterenol infusion. Retrograde conduction over the AP was studied in four of the remaining seven patients and was found to be present in three and absent in one. Although these patients differ from the ordinary patient with concealed AP in that antegrade preexcitation had been demonstrated in the past, this study suggests that concealed VP may result from the following mechanisms: 1) an extremely prolonged refractory period in the AP, causing a rate-dependent VP that can be identified during vagal stimulation; 2) a rate-independent depression of antegrade conduction that can be reversed by isoproterenol; 3) a depression of conduction that is apparently no longer reversible. Only in the latter case is a study of retrograde conduction needed to identify the concealed VP. These three mechanisms are likely to be a natural sequence of events leading to complete antegrade block in the AP.

A REMARKABLE advance in the knowledge of the Wolff-Parkinson-White syndrome (WPW) was the demonstration that an accessory pathway (AP) is capable only of retrograde conduction, and that under such conditions, arrhythmias occur without electrocardiographic evidence of ventricular preexcitation (VP). This has been termed "concealed or latent preexcitation" or "concealed WPW," as well as "concealed bypass" and "concealed AP." Diagnostic criteria are based on the existence of unidirectional block of the AP and include: 1) absence of VP pattern during normal sinus rhythm and during right and left atrial stimulation at different rates or coupling intervals and, if possible, from the proximal end of the AP; and 2) evidence of preserved retrograde conduction such as: a) eccentric right or left atrial preexcitation during ventricular stimulation; b) constant ventriculoatrial (VA) conduction time without refractoriness-dependent delay; and c) during paroxysms of reentrant tachycardia, VA conduction of a premature ventricular impulse discharged during the refractory period of the His bundle and d) increase in the cycle length of the tachycardia and the VA interval at the onset of bundle branch block homolateral to the AP. Some of these criteria are highly sophisticated and may require prolonged invasive manipulation.

If an AP is capable only of retrograde conduction, this may be related to two possible mechanisms: 1) a great prolongation of refractoriness and 2) a full depression of antegrade conduction, indicating that the safety margin for conduction is much narrower in the antegrade than in the retrograde direction. In the first instance, sufficient slowing of cardiac rate should reestablish antegrade conduction, as was the case in nine patients in whom VP was absent during sinus rhythm. In the second instance, we reasoned that the administration of a drug known to improve conduction, e.g., isoproterenol, could also restore antegrade conduction, as was true in five other patients. These observations indicate that simple, noninvasive maneuvers may uncover the existence of VP, and may elucidate mechanisms of so-called concealed preexcitation.

Material and Methods

Patients

Twenty-one patients with WPW were selected on the basis of having at least one previous ECG showing VP and recent tracing in which the VP pattern had disappeared either spontaneously or due to amiodarone, a drug known to depress conduction in the AP.

Table 1 summarizes the main clinical and electrocardiographic features. The eighth column refers to the time before study that an ECG showing VP was recorded (range 3 months to 20 years, average 50 months), and the next column describes the time before study when the ECG no longer showed VP (range 2 months to 5 years, average 25 months). In 10 patients the VP pattern disappeared spontaneously, and in the other 11 only after antiarhythmic therapy with amiodarone. Disappearance of VP was sustained during all the time described in the ninth column, as verified in three to 35 ECGs (average 12) recorded from each patient during such interval (last column). Although higher doses of amiodarone were administered initially, the dose indicated in the table was the one the patient was receiving at the time of the...
1. These study.

These patients differ from the ordinary patient with concealed AP in that antegrade preexcitation had been demonstrated in all of them in the past. However, they share with the so-called concealed preexcitation category the important feature that antegrade conduction over the AP had been persistently lost. Fifteen of the 21 patients were males. The WPW pattern was of the A type in 15 cases. The average age of the patients was 46 years and 4 months. Episodes of paroxysmal tachycardia had been recorded in 14.

### Diagnostic Procedures

Carotid sinus massage was performed in every patient during continuous ECG recording, in order to slow the heart rate or provoke long pauses, looking for reappearance of the VP. In 12 cases in which restitution of antegrade conduction over the AP did not occur, the same maneuvers were repeated every 1–2 minutes during the administration of an i.v. infusion of isoproterenol at progressively increasing doses of 1–4 μg/min for 10–20 minutes, and after discontinuing the infusion until the recorded changes returned to control conditions. In four of the seven patients in whom antegrade conduction over the AP was not restored by the preceding maneuvers, retrograde conduction was studied according to techniques reported by others.1-5, 8-13

In all cases in which VP reappeared, attempts were made to determine the duration of refractoriness in the AP. Conduction over the AP was uniformly rate-dependent. The antegrade refractory period of the AP was defined as the longest RR interval at which conduction failed in the AP and occurred only over the normal pathway. This measurement is equivalent to those previously reported by using the extrastimulus method at different cycle lengths.18-17 In the present case, however, because refractoriness was extremely prolonged, application of the extrastimulus method was not possible because the critical cycle length separating conduction from block in the AP was always longer than the spontaneous cycle length of each patient. For similar reasons and due to the unevenness of the vagal effects, control of the “preceding cycle length” was not possible. Therefore, in this study

### Table 1. Clinical Features of the 21 Patients Studied

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>WPW type</th>
<th>Clinical diagnosis</th>
<th>Tachyarrhythmias</th>
<th>Antiarrhythmic therapy</th>
<th>Last recorded ECG with WPW</th>
<th>First recorded ECG without WPW</th>
<th>ECGs without WPW (n)</th>
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<td>1</td>
<td>64</td>
<td>F</td>
<td>A</td>
<td>Systemic hypertension</td>
<td>PST</td>
<td>Amio 200 mg/day</td>
<td>3 yr, 6 mo</td>
<td>3 yr, 5 mo</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>38</td>
<td>M</td>
<td>A</td>
<td>—</td>
<td>PST</td>
<td>Amio 200 mg/day</td>
<td>2 yr, 1 mo</td>
<td>2 yr</td>
<td>15</td>
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<td>3</td>
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<td>A</td>
<td>Ischemic heart disease</td>
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<tr>
<td>4</td>
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<td>20 yr</td>
<td>3 yr</td>
<td>5</td>
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<td>58</td>
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<td>2 yr, 4 mo</td>
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<td>—</td>
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<td>—</td>
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<td>7 mo</td>
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<td>1 yr, 3 mo</td>
<td>1 yr, 2 mo</td>
<td>9</td>
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Abbreviations: Amio = amiodarone; Dig = digoxine; PST = paroxysmal supraventricular tachycardia; prop = propranolol; WPW = Wolff-Parkinson-White.
Table 2. Effects of Vagal Maneuvers and Isoproterenol on Antegrade Conduction in the Accessory Pathway

<table>
<thead>
<tr>
<th>Pt</th>
<th>Longest RR intervals during vagal stimulation</th>
<th>Shortest RR intervals during vagal stimulation at the time of I infusion</th>
<th>Longest RR intervals showing VP during I infusion</th>
<th>Shortest RR intervals showing VP during I infusion</th>
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<td>960</td>
<td>*</td>
<td>900</td>
<td>*</td>
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</table>

Values are given in milliseconds.

*Ventricular preexcitation was not restored.
†Isoproterenol was not administered.

Abbreviations: CSM = carotid sinus massage; I = isoproterenol; VP = ventricular preexcitation.

Refractoriness was a gross measurement of the duration of recovery in the AP.

Results

Effects of Vagal Stimulation

A typical VP pattern was recorded during vagal stimulation in nine of the 21 patients, at RR intervals of 930–1430 msec (table 2). Table 2 also describes the maximal diastolic pause provoked in all cases (range 760–5320 msec). In patients 10, 11, 12, 20 and 21, whom the provoked pauses were 760–1100 msec, the question remains whether conduction over the AP would not occur if longer RR intervals were induced. Figure 1 shows a representative example of vagal stimulation favoring reappearance of antegrade conduction over the AP. The first two beats show normal conduction (block in the AP) at a cycle length of 940 msec. During vagal stimulation, reappearance of VP occurs after pauses of 1300–1800 msec (third to fifth beats), and when carotid sinus massage is discontinued (arrow), the last two beats again show normal conduc-

Figure 1. Patient 9. Unmasking of ventricular preexcitation during the bradycardia provoked by carotid sinus massage (CSM). Leads I, II and VI are simultaneous. RR intervals are in milliseconds. See text for details.
tion after pauses of 1240 and 1120 msec, respectively. From this simple strip, refractoriness in the AP can be estimated at 1240–1300 msec, and it is clear that if pauses of the latter magnitude were not obtained, conduction over the AP could not be documented and the erroneous impression would be maintained that antegrade block in the AP was permanent. Figure 2 shows that the duration of refractoriness in the AP of these nine patients was 920–1420 msec. Two practical consequences can be derived. If pauses of such magnitude are not provoked in patients assumed to have concealed preexcitation, exploration of conduction over the AP is incomplete. Second, if VP does not occur after pauses of 1400–1500 msec, it is unlikely to occur at any other cycle length. Refractory periods longer than 1500 msec in the AP may eventually occur, but are probably uncommon.

**Effects of Isoproterenol**

Isoproterenol was administered only to the 12 patients in whom vagal maneuvers failed to reestablish conduction over the AP. During the infusion, conduction was restored in five of the 12 patients after pauses of 540–1040 msec (table 2). In three of these five subjects the duration of refractoriness in the AP was 540–1020 msec (fig. 3), while in the other two (patients 11 and 12), refractoriness could not be measured because it was shorter than the minimal RR interval during the isoproterenol infusion (540 and 580 msec, respectively). Refractoriness was clearly shorter in the five patients in whom conduction reappeared during isoproterenol administration than in the nine patients in whom conduction was restored by vagal stimulation alone. Figure 4 shows one of the isoproterenol studies. The upper strip shows normal conduction (block in the AP) at a spontaneous cycle length of 800 msec. During vagal stimulation (arrow), conduction is still normal after pauses up to 3200 msec. The three following strips recorded during the isoproterenol infusion show that VP occurred after pauses of 1040–1440 msec provoked by vagal stimulation (arrows). Two junctional escape beats are also shown. The two lower strips were recorded 3 and 10 minutes after discontinuation of the infusion; at 3 minutes, conduction over the AP occurred only after pauses of 1570–1600 msec, while at 10 minutes, conduction was again blocked, with return to the control conditions.

**Retrograde Conduction**

Retrograde conduction over the AP was studied in four patients in whom vagal stimulation and isoproterenol failed to restore antegrade conduction (cases 17, 18, 19 and 21). Retrograde conduction was shown in three by the occurrence of eccentric left atrial activation during ventricular stimulation and episodes of reentrant tachycardia provoked by the latter (case 18), or by a short and constant VA interval during ventricular pacing at different rates or coupling intervals of the ventricular extrastimulus (cases 17, 18 and 19). These three cases were thought to be genuine examples of total unidirectional block in the AP. In these three patients, the administration of an i.v. bolus of ajmaline, 1 mg/kg up to a maximum of 70 mg, caused a transient interruption of retrograde conduction, changing the unidirectional block into a bidirectional block (fig. 5). Ajmaline is a drug that depresses conduction in the AP, especially when conduction is naturally depressed. In one of the four cases (patient 21), retrograde conduction over the AP could not be documented. This was probably an example of naturally occurring total bidirectional block in the AP.
Discussion
Duration of Refractoriness in the Accessory Pathway

We have been able to show that simple maneuvers such as vagal stimulation and the administration of isoproterenol restored antegrade conduction over the AP in 14 of 21 selected patients who had apparent or real antegrade block. At that moment, antegrade conduction was rate-dependent and the duration of refractoriness was 920-1420 msec, with an average of 1136

Figure 4. Unmasking of ventricular pre-excitation during isoproterenol infusion in patient 13, in whom antegrade conduction was not restored by vagal stimulation alone. E = junctional escape. See text for details.

Figure 5. Demonstration of retrograde conduction over the accessory pathway in patient 19, in whom vagal stimulation and isoproterenol did not restore antegrade conduction. A) Simultaneous recording of an atrial electrogram and standard lead II during normal sinus rhythm. Atrioventricular conduction time is 160 msec. B) Ventricular pacing (S1) at progressively shorter cycle lengths from 670-410 msec showing a constant ventriculoatrial conduction time of 140 msec. A* = retrograde atrial activation. C) Regular ventricular pacing at a basic cycle length of 610 msec, and premature stimulation (S2) at progressively shorter coupling intervals between 510-410 msec. The ventriculoatrial conduction time remains constant. D) During regular ventricular pacing at a cycle length of 500 msec, the i.v. administration of 70 mg of ajmaline caused total interruption of retrograde conduction over the accessory pathway, and atrioventricular dissociation is observed.
msec in the nine patients in whom conduction was restored by vagal stimulation alone. This extremely prolonged duration of the antegrade refractory period of the AP should be contrasted with the much shorter duration reported by others. Durrer et al. described four cases with values of 270–365 msec. In 44 patients studied by Gallagher et al., refractoriness was 210–895 msec, but most values were 220–375 msec. In 107 patients studied by Wells, refractoriness was 180–700 msec. In 155 cases reported in these three studies, the longest refractory period (895 msec) was shorter than the shortest of our nine cases (930 msec).

This striking difference must reflect the fact that two different populations of WPW are being compared due to dissimilar patient selection. Our cases were specifically selected on the basis of a known pattern of VP that later disappeared, suggesting a spontaneous or drug-induced deterioration of conduction in the AP. Conversely, the 155 cases mentioned above, particularly because of their short refractory period, were obviously unlikely to develop antegrade block in the AP. It seems strange to us that in the 155 cases, refractoriness was never longer than 895 msec, perhaps reflecting a problem of methodology. Because all these patients were studied by atrial stimulation (which means a rate higher than the normal sinus rate), this excludes any case in which the refractory period of the AP is prolonged beyond 900–1000 msec. This view is supported by the relatively numerous cases of intermittent WPW occurring at normal cardiac rates (60–100 beats/min), in which refractoriness must last 600–1000 msec in order for the intermittency to occur. In 11 such cases, Denes et al. estimated the duration of refractoriness to be approximately (equal to sinus cycle length) 450–1020 msec. It is then reasonable to assume that, within an extremely wide spectrum, WPW with a greatly prolonged refractory period of the AP may be more common than previously thought and may be the basis of many cases of so-called concealed preexcitation. If cycle lengths longer than 900–1500 are not provoked, this mechanism may be totally ignored.

Mechanism of the Vagal Effect

The fact that a critical cycle length separating conduction from block was determined favors the interpretation that vagal stimulation acted merely by prolonging cycle length beyond the end of the refractory period. Although it is well known that the slowing of AV nodal conduction caused by vagal stimulation may provoke a "greater degree" of VP, this mechanism obviously could not explain the "reappearance" of VP in our patients. However, a direct vagal effect on the AP, though unlikely, cannot be totally disregarded. The fact that digitalis may shorten refractoriness in the AP, working with an isthmus of isolated canine atrial tissue simulating some of the features of preexcitation, showed that acetylcholine improved conduction under critical conditions. In addition, vagal stimulation may also enhance intra-atrial conduction, shift the site of impulse formation from the sinus node to an ectopic atrial focus and, as a consequence, produce a change in the mode and/or site of entry into the AP and the AV node. Wilson in 1915 and Wolff, Parkinson and White in 1930 had already shown that vagal stimulation favors the occurrence of VP. A single case in which the association of vagal stimulation and isoproterenol favored the occurrence of VP was reported by Gavrilcescu.

Mechanism of the Isoproterenol Effect

Catecholamines may improve conduction in depressed tissues by restoring a membrane potential reduced by stretch, hypoxia or toxic concentrations of ouabaine, and reverse the depressed conduction caused by toxic doses of procainamide and quinidine. The former effect has also been documented in human atrial tissue. A general improvement of conduction has also been shown to occur in the intact dog and in the presence of abnormal intraventricular conduction in the human. It is then natural to assume that in patients 13 and 14, in whom antegrade conduction in the AP was blocked even after extremely prolonged pauses (suggesting that block was due to a depression of conduction and not to a prolonged refractory period), the restoration of conduction caused by isoproterenol was probably due to a hyperpolarizing effect on a depressed AP. In patients 10, 11 and 12, in whom vagal stimulation did not provoke sufficiently long pauses, a greatly prolonged refractory period cannot be ruled out and, accordingly, it is also possible that isoproterenol restored conduction by shortening refractoriness. Isoproterenol may shorten refractoriness in both normal and depressed cardiac tissues, and it is then reasonable to assume that a number of patients who have resumed conduction in the AP during vagal stimulation would also have resumed conduction with isoproterenol. A shortening of the refractory period of the AP in three patients with WPW after the i.v. administration of 0.5 mg of orciprenaline (metaproterenol) has also been reported.

Implications

Our study allowed us to identify different groups of patients depending on the physiologic properties of the AP. One group included nine patients in whom the AP showed antegrade block that was rate-dependent and related to an extremely prolonged refractory period. These cases can be readily demonstrated by an appropriate slowing of the heart rate. A second group included at least two and probably three other patients in whom antegrade block was apparently rate-independent, but still reversible with isoproterenol. A third group included three patients in whom antegrade block was apparently irreversible, while retrograde conduction was preserved. These were the only genuine examples of complete unidirectional block in

*Because isoproterenol itself may shorten refractoriness, we do not include the cases in which the refractory period was measured during the isoproterenol infusion.
the present study. There was one patient in whom both antegrade and retrograde conduction were abolished. These groups of cases may be natural steps in the sequence of events leading to the development of complete antegrade block in the AP. Which one of these steps will in the future be considered as examples of concealed preexcitation is only a matter of semantics. More important is the fact that patients in whom AP antegrade block is suspected can sometimes be evaluated by simple clinical tests. The following protocol is presently used in our laboratory. First, vagal stimulation in order to provoke pauses of at least 1500 msec is attempted. If this does not disclose VP, we institute an isoproterenol infusion (combined with vagal stimulation). Only if these two steps fail to uncover VP is a catheterization study indicated in order to demonstrate the possible existence of retrograde conduction over an AP.

Limitations

One limitation of this type of study is that not all patients show sufficient slowing in response to vagal stimulation. There is certainly a need to develop more reliable techniques to slow the heart rate. It may also be argued that in too many cases the antegrade block in the AP was the result of administering a conduction-depressing drug. However, the effects of both vagal stimulation and isoproterenol were similar, regardless of whether the disappearance of VP occurred spontaneously or due to the action of amiodarone. Although our sample of patients was rather small, cases fulfilling the selection requirements of our material are not easy to collect. Further studies from other centers with similar types of patients may be needed in order to confirm the results presented in this paper.

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**Echocardiographic Evaluation of Mitral Stenosis Using Diastolic Posterior Left Ventricular Wall Motion**

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**SUMMARY** The slope of the posterior left ventricular wall motion in diastole (LVDS) was determined by echocardiography in 25 normal subjects and 21 patients with mitral stenosis. Patients with mitral stenosis had reduced LVDS that was related to the degree of mitral stenosis determined by calculated mitral valve area ($r = 0.92$). The mitral valve area correlated more closely with the LVDS than with the left atrial emptying index derived from the posterior aortic wall motion. Three patients with mitral stenosis had an increased LVDS after mitral valvotomy or mitral valve replacement. One patient with a stenotic mitral valve prosthesis had reduced LVDS. The results of this study suggest that analysis of the LVDS would be useful in predicting the severity of mitral stenosis and may be beneficial in evaluating patients with suspected prosthesis mitral valve malfunction.

**SINCE EDLER'S DESCRIPTION in 1955, M-mode echocardiography has been used to verify the presence of mitral valve stenosis with a high degree of accuracy.$^1$ Estimates of the severity of mitral stenosis using the diastolic closure rate of the anterior mitral valve leaflet (E-F slope) have not been accurate.$^2$ Strunk et al. suggested that because the motion of the posterior aortic wall in diastole reflects changes in the left atrial volume, analysis of this motion might allow more accurate assessment of the degree of mitral stenosis.$^3$ Hall et al.$^6$ found no correlation between the degree of mitral stenosis and the left atrial emptying index derived from the posterior aortic wall motion.

Volume changes within the left ventricle can be determined echocardiographically from analysis of the left ventricular wall motion. Alterations of the posterior left ventricular wall motion in diastole have been found in patients with impaired left ventricular filling from a variety of causes, including constrictive pericarditis, cardiac tamponade and hypertrophic cardiomyopathy.$^4$ Mitral stenosis, a condition with a reduced rate of left ventricular filling, might also be expected to show alterations of the posterior left ventricular wall motion on echocardiography. Accordingly, this study was undertaken to determine if patients with mitral stenosis had abnormal posterior left ventricular wall motion by echocardiography, and if so, whether analysis of this motion could be used to predict the severity of the stenosis.

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Received August 7, 1979; revision accepted October 17, 1979.
Circulation 61, No. 5, 1980.
Unmasking of ventricular preexcitation by vagal stimulation or isoproterenol administration.
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Circulation. 1980;61:1030-1037
doi: 10.1161/01.CIR.61.5.1030

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/61/5/1030