Procainamide and Retrograde Atrioventricular Nodal Conduction in Man

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SUMMARY Recent studies that show a depressant effect of procainamide (PA) on retrograde conduction in patients with atrioventricular (AV) nodal reentrant tachycardia (RT) have suggested possible incorporation of AV nodal bypass tracts. Electrophysiologic effects of i.v. PA, 10 mg/kg, on retrograde AV nodal conduction were examined in 13 patients without RT, demonstrable AV nodal refractory period curves, or accessory pathways. Ventriculoatrial (VA) conduction was recorded before and after PA using intracardiac electrograms, incremental ventricular pacing and extrastimulation. With incremental pacing during the control, VA block occurred at a mean cycle length (CL) of 364.6 ± 87.9 msec. After PA, VA conduction was abolished in five of 13 patients due to onset of retrograde block in the AV node; in seven of 13, VA block occurred at a longer paced CL after PA (344.2 ± 51.2 msec vs 477.1 ± 93.2 msec). In one patient, PA did not affect VA conduction. PA invariably produced prolongation in the VA interval at comparable CL of pacing. With ventricular premature stimulation, the retrograde H2A1 intervals during the control period were short (< 50 msec) in seven of 13, intermediate (60–100 msec) in three of 13 and long (> 100 msec) in three of 13 cases. PA either abolished H2A1 conduction (H2 but no A2) or prolonged the H2A1 intervals by 5–20 msec in most cases in this series. The data suggest that i.v. PA almost uniformly depresses retrograde AV nodal conduction in the intact human heart. This depressant response to PA is not indicative of presence of partial or complete AV nodal bypass tracts.

THE FUNCTIONAL CHARACTERISTICS of atrioventricular (AV) nodal conduction in the antegrade direction have been investigated. In contrast, rather limited information is available about the nature and functional behavior of retrograde AV nodal conduction in man. Although retrograde conduction has been studied in patients with so-called paroxysmal AV nodal reentrant tachycardia (RT), the nature of retrograde pathways in these patients is not clear. Recent studies showing a depressant effect of i.v. procainamide (PA) on retrograde conduction in patients with RT and dual AV nodal pathways raised some question about the nature of retrograde pathways in these cases. PA exerts a depressant effect on the His-Purkinje system (HPS) and accessory pathways (AP) and has minimal effect on antegrade AV nodal conduction. Thus, one may argue that depressant effect of PA on retrograde conduction in patients with RT implies participation of some form of partial or complete AV nodal bypass tracts. The effect of PA on retrograde AV nodal conduction should be known in patients without RT, demonstrable antegrade dual AV nodal refractory period curves, and retrogradely functioning AP of the Kent bundle type. This report describes functional behavior of retrograde AV nodal conduction before and after i.v. PA in 13 such patients. The implications of the electrophysiologic findings are discussed.

Patients and Methods

Thirteen patients (eight males and five females), ages 53–82 years (mean ± sd 66.2 ± 9.9 years), were studied because of recurrent ventricular arrhythmias, dizziness or syncope. Eight patients had arteriosclerotic heart disease and five had no clinically detectable heart disease. Ten had normal intraventricular conduction and three had right bundle branch block. Four patients had ventricular premature complexes and one patient had an old inferior myocardial infarction.

Patients gave informed, signed consent for the study.

Right-heart catheterization was performed in a nonsedated, postabsorptive state. With the patients under local anesthesia, quadripolar electrode catheters were percutaneously introduced through the femoral and antecubital veins and positioned under fluoroscopic guidance across the tricuspid valve near the AV junction to permit recording of the His bundle potential. The catheters were also advanced to the high right atrium and the right ventricle to permit recordings and electrical stimulation as previously described.

The intracardiac electrograms (filtered at 30–500 Hz) and three surface lead ECGs (usually leads I, II, and VI) and a time line were simultaneously displayed on a multichannel oscilloscope (Electronics for Medicine VR-12) and recorded on a magnetic tape (Honeywell model 96). Recordings were reproduced on photographic paper at 100 or 150 mm/sec. Electrical stimulation was performed using a digital stimulator (DTU; Bloom Associated, Ltd.).

During these studies, patients were isolated and all equipment was grounded at equipotential. The following protocol for electrical stimulation was performed: (1) incremental atrial pacing to achieve the antegrade AV nodal Wenckebach cycle; (2) antegrade refractory periods using atrial basic drive of eight beats (A1A1), followed by premature atrial stimulation (A2); (3) incremental ventricular pacing to achieve ventriculoatrial (VA) block; and (4) retrograde refractory
periods using ventricular basic drive of eight beats (S1S2 or V1V1), followed by premature ventricular stimulation (S2 or V2).

**Definitions and Measurements**

Definitions for antegrade and retrograde conduction and refractory periods have been published. Pertinent definitions used in this report are described below.

**Retrograde Conduction**

VA or SA interval was measured from the corresponding stimulus artifact to the onset of the low right atrial deflection on the His bundle electrogram (HBE) and high right atrial (HRA) deflection on local electrogram. Since the main objective was to measure the retrograde AV nodal conduction as accurately as possible, the VA on the HRA electrogram was only measured when the onset of low atrial deflection on the HBE could not be clearly separated from the local ventricular electrogram. In these latter cases, when the onset of low atrial (A2) deflection was clearly separated from V2 during ventricular premature stimulation, the interval between the onset of low right atrial and HRA deflections was subtracted from the VA interval on the HRA electrogram. This method permitted reasonably accurate (although indirect) estimation of VA interval for the HBE for all paced cycle lengths (CLs) because no intraatrial delay was noted in these patients. After the retrograde H2 deflection emerged from the local V2, retrograde HPS conduction times were measured from the corresponding stimulus artifact to the onset of the retrograde H2 deflection and retrograde AV nodal conduction was measured from both the onset and the end of H2 to the beginning of A2 deflection on the HBE.

**Retrograde Refractory Periods**

Effective refractory period (ERP) of ventricular myocardium (VM). The longest S1S2 that fails to evoke V2.

ERP of the HPS. The longest V1V2 at which V2 blocks within the HPS.

Functional refractory period (FRP) of the HPS. The shortest S1H2 (or V1H2) interval in response to a full range of S1S2 intervals. S1H2 was taken in lieu of retrograde H1H2 because retrograde H1 is generally not identifiable and data from animal and a few human studies indicate that S1H1 interval remains constant. Therefore, the S1H2 value is expected to exceed the H1H2 interval by a fixed amount. To assess the effect of prematurity on retrograde H2A2 conduction, this measurement is more pertinent than the prematurity of V1V2 due to intervening HPS, an area of significant conduction delay during retrograde propagation of impulses.

**Intravenous Procainamide**

After initial studies, all patients received PA, 10 mg/kg intravenously, while the blood pressure was carefully monitored and no significant hypotension was encountered. In all cases the repeat protocol was completed in 15 minutes of PA. Blood samples for PA levels were drawn before and after PA. Plasma PA concentrations were within therapeutic range of 4.2-9.8 µg/ml (mean 5.8 ± 1.8 µg/ml) as measured by gas chromatography. The therapeutic level for our laboratory is 4-8 µg/ml.

Statistical analysis of data was done using a t test for paired data.

**Results**

Complete antegrade and retrograde conduction and refractory period data are available in all cases, but only relevant data are presented here.

**Antegrade Conduction Times and Refractory Periods**

The effects of i.v. PA on sinus CL, antegrade conduction, and refractory periods were similar to those published previously. The mean control spontaneous sinus CL AH interval during sinus rhythm, as well as the CL of atrial pacing that induced AV nodal Wenckebach phenomenon, demonstrated a small but insignificant shortening. PA consistently prolonged the HV interval (control 46.1 ± 5.8 msec; PA 60.7 ± 9.0 msec); however, no further prolongation occurred during incremental atrial pacing up to rates resulting in AV nodal Wenckebach cycles. The effect of PA on the FRP and ERP of the AV node was variable and statistically insignificant; however, overall, the mean values showed a slight decrease. The ERP of the atrium increased in all patients.

**Retrograde Conduction (table 1)**

The control CL that produced VA block was 364.6 ± 87.9 msec before PA. After PA, VA conduction was abolished in five of 13 cases (patients 2, 6, 7, 11

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All measurements are in milliseconds.

Abbreviations: C = control; PA = procainamide; CL = cycle length; VA = ventriculoatrial conduction; LRA = low right atrium; S = stimulus.
and 13) (fig. 1). That the site of retrograde block was the AV node was suggested by block of dissociated sinus beats proximal to the His deflection. In patients 1, 3, 4, 8, 9, 10 and 12, the ventricular CL required to produce VA block was longer (344.2 ± 51.2 msec vs 477.1 ± 93.2) (fig. 2). In patient 5, the onset of VA block occurred at the same CL (260 msec) before and after PA. During control, the shortest VA intervals were 151.9 ± 51.9 msec (range 85–285 msec) and remained constant with incremental pacing in patients 4, 7, 9 and 10, whereas the other patients showed progressive prolongation of VA. In the eight patients who retained intact VA conduction after PA, the shortest VA intervals were prolonged by a mean of 32.5 ± 22.0 msec (range 10–80 msec) after PA. Similarly, the longest VA intervals with 1:1 VA response were also increased by a mean of 41.2 ± 19.4 msec after PA. The site of retrograde conduction delay, i.e., above or below the His, during 1:1 VA response after PA could not be directly determined in most cases. However, in patients 1, 4 and 5, the retrograde His potential could be identified during the basic drive and the HA prolongation and block in response to PA could be directly documented in these cases (fig. 2). In five cases, the longest VA intervals after PA exceeded the control values by 25 msec or more. Even if PA produced VH prolongation (similar to HV lengthening) in these cases, the magnitude of the VA-interval increase suggests that concomitant prolongation of HA intervals existed. This could be directly documented during retrograde refractory period studies. In this series of patients who maintained intact VA conduction after PA, the control shortest VA values were not different than those in patients who displayed complete retrograde AV nodal block after PA.

Retrograde Refractory Periods (table 2)

During the control period, A2 activation occurred in all patients and was preceded by His deflection. At shorter V1H2 intervals, the retrograde H2A2 either remained constant or a prolongation was noted, suggesting that retrograde A2 activation was dependent upon retrograde H2 depolarization (fig. 3). In all patients except patient 9, the retrograde H2 deflection eventually emerged from the V2 electrogram after PA, indicating integrity of retrograde conduction up to the His bundle. As expected, the S2H2 intervals (i.e., retro-
grade HPS conduction times) at comparable S1S2, the longest S2H2 as well as the values of ERP-VM after PA exceeded the control values. Similarly, the shortest S1H2 intervals after PA were also consistently longer than the control values, indicating an increase in the FRP of the HPS. During the control period, the retrograde H2A2 intervals (as measured from the onset of H deflection) were relatively short (≤ 50 msec) in

### Table 2. Refractory Period Studies Before and After Procaainamide

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All measurements are in milliseconds.

*Basic cycle lengths were the same before and after PA.

Abbreviations: C = control; PA = procaainamide; B-AVN = blocked at atrioventricular node; VA = ventriculoatrial; ERP of HSP = effective refractory period of His-Purkinje system; ERP of VM = effective refractory period of ventricular myocardium.
that site of retrograde block was above the H₂. In patients 3–5, 10 and 12, V₂A₂ conduction remained intact after PA. Patients 3, 5, 10 and 12 showed a 5–20-msec increase in H₂A₂ after PA. The H₂A₂ increase after PA was noted despite significantly longer S₁H₂ intervals (45–90 msec longer than controls). Patient 5 showed no detectable changes in H₂A₂ conduction after PA. In case 9, no retrograde H₂ deflection was identified after PA, making it difficult to assess the site of retrograde delay and block.

Discussion

The characteristics of retrograde conduction in the HPS both before and after PA in this study were similar to those previously described.8,11,14,16 As expected, retrograde conduction and refractoriness of HPS and ventricular myocardium increased after PA. However, the depressant effect of PA on retrograde HA conduction in the form of delay or complete block was obvious and could be directly documented during ventricular premature stimulation. Simultaneous assessment of antegrade conduction in this study also revealed that whereas PA had insignificant effect on antegrade AV nodal conduction, it depressed HA conduction in almost all patients.

Significance of Depressant Effect of PA on Retrograde Conduction

Since PA is known to have depressant effect on HPS and AP of the Kent bundle type, an obvious question arises as to whether antegrade and retrograde conduction in these cases occurred along the same anatomic pathway.11,12 In the antegrade direction, the functional behavior was typical of AV nodal conduction in the absence of demonstrable discontinuous refractory period curves.4–8 In the retrograde direction, atrial activation (A₂) was dependent upon retrograde H₂ activation, suggesting lack of participation of an AP of the Kent bundle type. However, the possibility of extranodal AP with long VA conduction in patients 11–13 and use of partial and/or complete AV nodal (His-atrial) bypass tracts in the remaining cases cannot be excluded.25,6,18–21 Most reports suggesting or demonstrating use of retrogradely functional bypass tracts with either long or short VA intervals were in patients with spontaneous or laboratory-induced atrial reciprocal beats or supraventricular tachycardias.7,8,19,20 None of the cases in this series had historical, electrocardiographic or electrophysiologic evidence of functioning antegrade or retrograde extranodal AP. Patients with spontaneous or laboratory-induced atrial echo beats or supraventricular tachycardias were specifically excluded so that we could study patients with the least likelihood of functioning AP. The actual anatomic existence of partial or complete AV nodal (atrial–His) bypass tracts in the human heart has been questioned.22 Furthermore, patients in this series had a full range of VA and HA intervals, from 30–235 msec. If VA conduction in these patients is not representative of conduction through the normal pathway (i.e., HPS-AV node), VA conduction through the normal pathway

**Figure 3.** Retrograde refractory period curves before and after procaainamide (PA) in patient 3. At a basic cycle length of 700 msec, the retrograde S₁H₂ and H₂A₂ intervals in response to progressively shorter S₁S₂ intervals are shown both before and after PA. The H₂A₂ intervals remain constant before and after PA in response to the full range of S₁H₂ intervals, suggesting retrograde A₂ activation via H₂. The H₂A₂ values are longer after PA despite longer S₁H₂ intervals. ERP–VM = effective refractory period of the ventricular myocardium.

patients 1 and 3–8, long (≥ 100 msec) in patients 11–13 (fig. 4), and of intermediate duration (60–80 msec) in patients 2, 9 and 10. Before PA, none of the patients in this series demonstrated a retrograde block of V₂ above the His bundle during ventricular premature stimulation. After PA in patients 1*, 2, 6, 8 and 11, when no VA conduction was noted either during the basic drive or the premature stimulation, the initial site of block after V₂ was above the H₂ deflection. Patients 7 and 13 had intact VA during the basic drive after PA; however, V₂ blocked (i.e., no A₂) before H₂ emergence from V₂ and therefore the H₂A₂ intervals after PA could not be measured. The retrograde H₂ deflection did emerge from V₂ at closer V₁V₂ without resumption of V₂A₂ conduction, confirming

*When refractory period studies were being performed, complete VA block was noted in patient 1 and VA conduction had resumed in patient 13.
probably does not exist. However, until further evidence is available, we must assume that VA conduction in this group of cases occurred by way of the HPS-AV node.

Determination of Retrograde Conduction Through the AV Node

Criteria to determine retrograde conduction through the AV node are indirect and primarily based upon the exclusion of AP participation and have been mainly described in cases with paroxysmal supraventricular tachycardia.7–9, 19, 20, 23, 24 When AP incorporation cannot be demonstrated, retrograde conduction is assumed to be through the AV node. Findings suggestive of conduction through the AV node, such as progressive prolongation of VA conduction time, occurrence of ventricular echo phenomena and sequence of atrial activation, all have limitations.18 In the present series, PA had comparable depressant effect on patients with constant VA vs those who demonstrated progressive prolongation. Similarly, PA produced depression of HA conduction in patients with short, medium and long HA intervals. Thus, if retrograde partial or complete AV nodal bypass tracts were present in any of these patients, the response to PA could not identify such cases.

Electrophysiologic Implications

Although this study does not provide definitive answers about the nature of retrograde pathways, the results do raise important issues. There is insufficient information to describe the behavior of retrograde AV nodal conduction in the intact human heart. One question is whether one needs to invoke anatomically distinct pathways to explain differences of conduction or different responses to drugs during impulse propagation in the two directions.5, 18, 26 Previous work in animals suggests that a disparity of conduction in opposite directions in the same tissue can be produced by changes in local geometry relative to the direction of
impulse propagation. Using sheep Purkinje fibers, Downer and Waxman et al. demonstrated that unidirectional block was predictably induced by focal cooling in either direction by altering the geometry of the lesion. They suggested that an impulse encountering a gradually rising threshold was more likely to block than an impulse that abruptly encounters a zone of inexcitable cells. In the latter case, a small space constant and readily excitable cells on the other side of block may allow regenerative response from electrotonic spread of a blocked impulse. Unidirectional block represents an extreme form of disparity in conduction in the two directions and occurs both in the AV node and AP of the Kent bundle type and was noted in five of 13 cases after PA in this series. Such unidirectional preferential conduction cannot be explained by gross anatomic variations or discontinuity of tissues, particularly when intermittency of conduction can be demonstrated, as in intermittent ventricular preexcitation.

De la Fuente et al. proposed another physiologic mechanism of block they termed as impedance mismatch, in which an impulse blocks at the junction of narrow isthmus with a longer mass of the same tissue while traveling toward the larger area. Such an impedance mismatch may be more (or less) likely to occur if there was tissue mismatch as well, as for example, between atrial vs His-nodal junction. A better margin of safety for impulse propagation for retrograde (vs antegrade) direction across the Purkinje-muscle junction and the two directions in the AV node has been partly attributed to the peculiarities of the geometric arrangements of fibers. Approaches to the AV node, the geometric arrangement of fibers, impedance and tissue mismatch may affect impulse propagation across the AV node. This could explain the differences in antegrade and retrograde conduction across the AV node as well as different responses to the drugs. Although these explanations are hypothetical and obviously cannot be explained from the data presented, they deserve further exploration.

Acknowledgment

We gratefully acknowledge the assistance of Debby Carlone, Kathryn Corriere, and Robert Walters.

References

Electrophysiologic Characteristics of Human Ventricular and Purkinje Fibers

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Summary: We studied the electrophysiologic characteristics of ventricular muscle and Purkinje fibers from the hearts of five patients undergoing cardiac transplantation. All five patients had congestive failure and coronary artery disease before surgery and were receiving digoxin therapy. Ventricular muscle had a maximal diastolic potential (MDP) of -78 ± 1 mV (mean ± SEM), an action potential (AP) amplitude of 104 ± 2 mV, a phase 0 upstroke velocity (\(V_{\text{up}}\)) of 297 ± 19 V/sec and an AP duration at 50% repolarization (APD\(_{50}\)) of 190 ± 4 msec. Purkinje fibers had an MDP of -80 ± 2 mV, an AP amplitude of 107 ± 2 mV, a \(V_{\text{up}}\) of 388 ± 25 V/sec and an APD\(_{50}\) of 195 ± 9 msec. Fibers from infarcted sections of the heart had significantly longer APD than those from noninfarcted and adjacent zones. Both epinephrine and ouabain induced delayed afterdepolarizations in Purkinje fiber. This suggests that delayed afterdepolarizations and resultant triggered activity can occur in the human ventricle.

Methods

Hearts were obtained from five patients at cardiac transplantation. Informed consent was obtained from each patient.

Patient 1 was a 49-year-old female who had acute rheumatic fever at 19 years of age and an acute myocardial infarction at 45 years of age, followed by coronary artery bypass surgery. Congestive heart failure developed and was treated with digoxin, but her health continued to deteriorate; during the 6 months before her cardiac transplantation she had two episodes of ventricular fibrillation. Before transplantation, severe biventricular failure with poor contractility of both ventricles was demonstrated. Her medications included digoxin, quinidine and, just before surgery, lidocaine.

Patient 2 was a 15-year-old female in whom tetralogy of Fallot was diagnosed at 3 months of age. At 4 months of age she underwent a shunt procedure to increase pulmonary blood flow. Approximately 2 years before cardiac transplantation she began having episodes of hemoptysis. Cardiac catheterization revealed an occluded shunt and she underwent open heart repair of tetralogy of Fallot, during which she had a large anterolateral myocardial infarction. Subsequently, cardiac catheterization revealed severe right and left ventricular dysfunction and a large anteroapical aneurysm. Because of persistent severe congestive failure, cardiac transplantation was performed. Her medications before transplantation were digoxin and furosemide.

Patient 3 was a 48-year-old male who had an acute myocardial infarction at 41 years of age. One year later, he had left ventricular failure that required digoxin and diuretics. Five months before transplantation, coronary angiography showed complete occlusion of the right coronary artery and a 60% proximal occlusion of the left anterior descending artery. Because of severe coronary artery disease deemed not remediable by bypass techniques, and severe cardiomyopathy, cardiac transplantation was performed.

Patient 4 was a 48-year-old male who had his first myocardial infarction at the age of 43 years. This was

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