Demonstration of a Left Atrial Input to the Atrioventricular Node in Humans

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Background—During right atrial stimulation, the anterior and posterior approaches provide inputs to the atrioventricular (AV) node. The purpose of the present study was to determine how activation proceeding from the left atrium reaches the AV node.

Methods and Results—We studied AV nodal conduction during right and left atrial (coronary sinus) stimulation in 46 patients (27 women and 19 men; mean age, 46±4 years) who had structurally normal hearts. At an identical cycle length (600 ms), left atrial stimulation resulted in shorter A-H intervals than right atrial stimulation (73±3 ms versus 99±3 ms; P<0.05). In addition, atrial electrograms recorded close to the His bundle changed from near to far field potentials when stimulation was shifted to the left atrium. The A-H interval prolonged as the site of pacing was progressively moved from the distal to the proximal coronary sinus. During constant pacing from the distal coronary sinus, atrial activation close to the His bundle could be advanced by late extrastimuli delivered at the anterior and posterior approaches (up to 11±2 ms and 9±1 ms, respectively), without altering His bundle activation time. In contrast, late extrastimuli delivered at the inferoparaseptal mitral annulus advanced both the A and H electrograms in 19 of 20 patients, which is consistent with a left-sided input to the AV node. Right and left atrial stimulation resulted in similar AV nodal function.

Conclusion—The mitral annulus provides a left atrial input to the human AV node. (Circulation. 2002;106:2930-2934.)

Key Words: atrioventricular node ▪ atrium ▪ conduction ▪ electrophysiology ▪ mapping

Several studies have determined that the anterior and posterior approaches provide the main inputs to the atrioventricular (AV) node for activation proceeding from the right atrium.1–3 Whether activation originating from the left atrium enters the AV node using the same approaches (through interatrial connections4–6) or a still-undetermined left atrial input is unknown.7,8 Several observations suggest the presence of additional inputs to the AV node. For example, ablation of the anterior and posterior approaches in dogs rarely causes complete AV block,9 and a recent histological study in human hearts10 demonstrated the presence of both rightward and leftward extensions of the AV node reaching the tricuspid annulus and mitral annulus, respectively. On the basis of these observations, we hypothesized that the mitral annulus could provide a left atrial input to the AV node. Hence, the purpose of the present study was to investigate whether activation proceeding from the coronary sinus and adjacent left atrium enters the AV node through the fossa ovalis and anterior approach (Figure 1), through the coronary sinus musculature and posterior approach, or directly through the mitral annulus.

Methods

Patients

Forty-six patients (27 women and 19 men; mean age, 46±4 years) who had structurally normal hearts and were referred for radiofrequency catheter ablation were included in the study. Patients with first-degree AV block or a relative refractory period of the AV node >570 ms were excluded. Twenty-four patients were studied before radiofrequency catheter ablation (diagnosis included AV nodal reentrant tachycardia in 13 patients, right atrial tachycardia in 7 patients, and atrial flutter in 4 patients). Twenty-two patients were studied after radiofrequency catheter ablation (diagnosis included left-sided accessory AV pathway in 14 patients, focal atrial fibrillation in 6 patients, and right ventricular outflow tract tachycardia in 2 patients). The study protocol was approved by the University of Florida Institutional Review Board, and each patient gave written informed consent.

Electrophysiological Study

Patients were studied in a drug-free state under sedation with intravenous fentanyl and midazolam. Multipolar electrode catheters were introduced percutaneously and positioned in the right atrial appendage, right ventricle, His bundle region, and coronary sinus. To record His bundle activation, a 7-French deflectable catheter with 4...
closely spaced (2-mm) pairs of electrodes (Cordis Webster) was used. A deflectable catheter with 8 pairs of electrodes (2-mm interelectrode distance and 5 mm between pairs of electrodes; Cordis Webster) was advanced into the coronary sinus, with the most proximal pair of electrodes positioned at the coronary sinus ostium. Localization of the ostium was facilitated by observing, in the left anterior oblique projection (Figure 1), the entry point into the coronary sinus of a mapping catheter withdrawn with clockwise rotation from the isthmus. In patients who required access to the left atrium, a mapping catheter was introduced using trans-septal left heart catheterization.11

Right Atrial and Coronary Sinus Stimulation
The A-H intervals and the characteristics of the atrial electrograms recorded close to the His bundle were studied during pacing at a constant cycle length of 600 ms from the right atrial appendage and from the left atrium (distal coronary sinus). Thereafter, the site of stimulation in the coronary sinus was moved proximally in 5-mm steps until it was performed from each of the 8 pairs of electrodes. To study AV nodal function, decremental stimulation (10 ms steps) was performed from the distal coronary sinus and from the right atrial appendage until Wenckebach block proximal to the His bundle was induced. Similarly, the relative, functional, and effective refractory periods of the AV node were determined during both right and left atrial stimulation.12

Late Extrastimuli Delivered During Coronary Sinus Stimulation
To determine whether a site was part of the activation path reaching the AV node, we adapted the entrainment technique.13,14 During constant stimulation from the distal coronary sinus (S1-S1=600 ms), late atrial extrastimuli (S2) were delivered every eighth paced beat at the anterior approach (n=46), posterior approach (n=46), and inferoparaseptal mitral annulus (n=20). Stimulation of the anterior approach was obtained by positioning a pacing catheter just posterior to and to the left of the catheter recording the His bundle at the level of the tendon of Todaro.15 Stimulation of the posterior approach was performed from the coronary sinus ostium. The mitral annulus was stimulated using the trans-septal approach with a catheter curved so that the tip was located at the inferoparaseptal mitral annulus. Initially, extrastimuli were introduced immediately after the local electrogram. The coupling interval was then shortened in 2-ms steps to progressively advance the local atrial electrogram, the atrial electrogram recorded close to the His bundle, and eventually His bundle activation. Stimuli were of 1-ms duration and delivered at twice the diastolic threshold.

Definitions
The A-H interval was measured from the initial deflection of the atrial electrogram (far or near field) to the initial deflection of the His bundle electrogram. A site was considered part of the wavefront reaching the AV node during coronary sinus pacing when minimal pre-excitation (2 ms) of the atrial electrogram recorded close to the AV node was followed by identical pre-excitation of the His bundle. In addition, progressively earlier extrastimuli also resulted in similar pre-excitation of atrial and His bundle activation (4 ms, 6 ms, 8 ms, etc).

Data Analysis
Data are reported as mean±SEM. Mean values obtained at each of the 8 stimulation sites along the coronary sinus and at the right atrial appendage were analyzed using repeated measures ANOVA followed by Tukey pairwise testing. The 3 entrainment sites were compared using Kruskal-Wallis ANOVA followed by pairwise multiple comparison (Dunn’s method). \( P<0.05 \) was accepted as statistically significant.

Results
The A-H Interval During Right Versus Left Atrial Stimulation
Figure 2 illustrates the A-H interval shortening and changes from near to far field atrial potentials when the stimulation site was switched from the right atrium to the distal coronary sinus. In all patients, distal coronary sinus stimulation resulted in a significant shortening of the A-H interval when compared with right atrial stimulation (73±3 ms versus 99±3 ms).
ms; $P<0.05$; Figure 3). In 3 patients, the A-H interval could be recorded simultaneously from the left (retrograde transaortic approach) and right side of the heart during right atrial versus coronary sinus stimulation. Similar intervals were recorded on both sides of the AV septum (data not shown).

The A-H Interval and Coronary Sinus Pacing Site
A progressive prolongation of the A-H interval was observed as the pacing site in the coronary sinus was shifted proximally (ANOVA, Tukey test, $P<0.05$). Figure 3 depicts the mean A-H interval during constant pacing at the right atrial appendage and at each site along the coronary sinus. Distal coronary sinus stimulation resulted in an A-H interval that was $11 \pm 1$ ms shorter than that with proximal coronary sinus stimulation and $25 \pm 2$ ms shorter than that with right atrial stimulation ($P<0.05$).

Entrainment During Distal Coronary Sinus Stimulation
In Figure 4, a late extrastimulus delivered at the anterior approach (Figure 1) resulted in pre-excitation and change in the characteristics of the atrial potentials recorded close to the His bundle. However, His bundle activation time remained unchanged. Similar findings were observed using extrastimuli delivered at the posterior approach. In contrast, extrastimuli delivered at the inferoparaseptal aspect of the mitral annulus (Figure 5) simultaneously advanced both atrial and His bundle electrograms without changes in the characteristics of the atrial potentials recorded close to the His bundle. Figure 6 depicts the maximal atrial pre-excitation obtained from each site without His bundle pre-excitation in the study group. Atrial electrograms could be dissociated from nearby His bundle potential in all 46 patients with extrastimuli delivered at the anterior approach ($11 \pm 2$ ms; median, 10 ms; range, 4 to 24 ms), in 45 of 46 patients with extrastimuli delivered at the posterior approach ($9 \pm 1$ ms; median, 9 ms; range, 0 to 18 ms), and in 1 of 20 patients with extrastimuli delivered at the mitral annulus ($0.3 \pm 0.2$ ms; median, 0 ms; range, 0 to 4 ms), respectively ($P<0.001$).

AV Nodal Function During Right Versus Left Atrial Stimulation
Right and left atrial stimulation resulted in similar AV nodal function (Wenckebach cycle length, $370 \pm 9$ ms versus $369 \pm 9$ ms; effective refractory period, $300 \pm 11$ ms versus $307 \pm 9$ ms; functional refractory period, $385 \pm 13$ ms versus $386 \pm 12$ ms; relative refractory period, $562 \pm 2$ ms versus $564 \pm 3$ ms).

Discussion
The present results demonstrate that the mitral annulus provides an input to the human AV node that is independent of the inputs supplied by the anterior and posterior approaches.1–3

Previous Studies Suggesting a Left Atrial Input to the AV Node
Several published observations are consistent with the present findings. First, anatomical studies have demonstrated that the human AV node, although frequently depicted as a rightsided structure, is in fact located in the AV septum, with extensions reaching the tricuspid and mitral annuli.10 Second, in the canine heart,16 interruption of the posterior approach to the AV node can shift retrograde atrial activation to the left atrium. Third, in the swine heart, persistence of AV conduction from the left atrium has been shown in some animals after ablation of all interatrial connections.17 However, despite these findings, a left atrial input to the AV node has not been previously demonstrated in humans.
Shortening of the A-H Interval During Coronary Sinus (Left Atrial) Stimulation

Consistent with a previous study, 18 we found that the A-H interval is similar when recorded simultaneously from the left and right side of the heart during coronary sinus stimulation. Therefore, the shorter A-H interval cannot be explained by poor recording from the right side of far-field potentials originating from the left side. A more likely explanation is that the left atrial wavefront propagates perpendicular and not parallel to the AV node/His bundle axis, reaching the right side of the AV septum when depolarization of the AV node is already in progress.

Two previous reports documented (although not consistently) a shorter A-H interval during coronary sinus stimulation 7,8 that was associated in one study with a shorter Wenckebach cycle length. 7 This finding was interpreted as enhanced AV nodal conduction or partial bypass of the AV node. In contrast, the present study demonstrates that the shorter A-H interval during coronary sinus stimulation is the result of activation via a different atrial input to the AV node. However, conduction via the posterior approach can also result in a shorter A-H interval. 19,20 In the present study, the gradual prolongation of the A-H interval as the pacing site was moved distally to proximally along the coronary sinus and the results obtained with extrastimuli indicate that the coronary sinus and the posterior approach were not part of the activation pathway reaching the AV node in most patients. Furthermore, the progressive A-H interval prolongation when the pacing site was moved proximally along the coronary sinus probably represents a gradual shift between 2 atrial inputs (mitral annulus to posterior approach).

Use of Late Extrastimuli to Identify a Left Input to the AV Node

To our knowledge, no previous work has applied the use of late extrastimuli to identify anatomical regions that may or may not serve as inputs to the AV node during atrial stimulation. This technique is frequently used to identify sites that participate in reentrant tachycardias. 13,14 In the present study, the same concept was applied to determine the wavefront path reaching the AV node during coronary sinus stimulation. Using this technique, the posterior and anterior approaches, but not the mitral annulus, could be dissociated from His bundle activation in most patients, consistent with a left-sided input to the AV node.

Limitations

The entrainment technique is typically used during reentrant tachycardias to determine if a site is part of the reentrant circuit. 13 In the present study, the procedure was modified to identify the path reaching the AV node during constant stimulation and not during tachycardia. Because of potential shortcomings of the present methodology, we cannot entirely rule out the possibility that a nearby structure, and not the mitral annulus itself, provides the left atrial input to the AV node. Although very late extrastimuli were used to test potential inputs to the AV node, cycle length-dependent conduction delay in the AV node could have occurred. Under these conditions, a prolongation in the AV nodal conduction time might have prevented pre-excitation of His bundle activation, resulting in a longer than expected H-H interval for a given A-A interval. The fact that minimal pre-excitation of the mitral annulus (but not the anterior or posterior

Figure 5. Extrastimulus (S2) delivered at the inferoparaseptal aspect of the mitral annulus (MA) during constant stimulation (S1) from the distal coronary sinus (CS) advanced both the A and His bundle electrograms (A-A = 590 ms; H-H = 590 ms), without altering the morphology of the atrial electrogram recorded close to the His bundle. RAA indicates right atrial appendage; HB, His bundle; MA, mitral annulus; CS, coronary sinus; A, atrial electrogram recorded close to the His bundle; H, His bundle electrogram; p, proximal; and d, distal.

Figure 6. Bar graphs identify 3 sites where late extrastimuli were delivered during constant distal coronary sinus stimulation. Each bar depicts maximal pre-excitation in milliseconds (ms) of atrial activation recorded close to the His bundle without altering His bundle activation time. AA indicates anterior approach; PA, posterior approach; and MA, mitral annulus.
approaches) resulted in simultaneous pre-excitation of the A and H potentials in 19 of 20 patients argues against significant cycle length-dependent conduction delay.

Finally, the conduction characteristics of the left-sided input at different cycle lengths were not studied to minimize decremental conduction. Therefore, the present study did not determine if this input has fast or slow AV nodal pathway properties.

Clinical Implications
This study identifies an input to the AV node proceeding from the mitral annulus that could represent the functional counterpart of the leftward posterior extension of the AV node described by Inoue and Becker. A left atrial input could not only provide a greater margin of safety for AV nodal conduction, but also have a role in reentrant tachycardias. For example, ablation at the mitral annulus can successfully eliminate certain forms of AV nodal reentrant tachycardia.

Further studies are required to elucidate the role of the left atrial input in normal and abnormal AV nodal conduction and the participation of this input in reentrant tachycardias involving the human AV node.

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