Slow Potentials in the Atrioventricular Junctional Area of Patients Operated on for Atrioventricular Node Tachycardias and in Isolated Porcine Hearts

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Objectives. The purpose of this study was to 1) investigate extracellular electrograms in the atrioventricular (AV) junctional area of patients with AV node reentrant tachycardia, 2) compare them with recordings made in isolated porcine hearts, and 3) study their origin.

Background. Electrograms with slow components have been used to target the delivery of radiofrequency energy for the cure of AV node reentrant tachycardia. The origin of these electrograms is unknown.

Methods. In 12 human and 19 porcine hearts, extracellular recordings were made simultaneously from 64 sites. In five other porcine hearts, intracellular recordings were made at sites at which extracellular electrograms revealed slow potentials. Histologic investigations were carried out in four of these hearts.

Results. Electrograms with slow components were recorded in five human and eight porcine hearts. These signals were found at sites up to 12 mm from the His bundle. Characteristics of the electrograms did not differ significantly among human and porcine hearts. Electrophysiologic evidence for multiple pathways was present in four hearts. Superficial impalements with microelectrodes at sites with slow potentials showed action potentials with AV node characteristics. In the majority of these recordings, the upstroke coincided with the downstroke of slow potentials. Histologic investigations of the sites of impalement revealed transitional cells directly underneath the endocardium.

Conclusions. Slow potentials were recorded in both human and porcine hearts in similar measure. They arise from transitional cells and have action potentials similar to N cells.

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Atrioventricular (AV) node reentrant tachycardia is due to reentry in the region of the AV node. These tachycardias may be cured by a variety of surgical or catheter ablation techniques (1–7). Anatomic landmarks and electrical activation sequence mapping have been used to guide these procedures. Recently, it has been suggested that the morphology of extracellular electrograms may be used to target the delivery of radiofrequency energy to the site of the "slow pathway" (8,9), a component of the reentrant circuit. Jackman et al. (8) and Haissaguerre et al. (9) have suggested that electrograms recorded from successful ablation sites have specific morphologic features. The origin of these potentials is unknown.

Intracellular and extracellular measurements have been carried out in superfused preparations of the AV node of rabbit and canine hearts (10). Extracellular recordings have been made from the AV node of the intact bovine and canine heart (11–13) and during catheter mapping in humans (8,9). The results provide a basis for expecting the possibility of recording extracellular signals with an AV node origin from the AV junctional area.

The purpose of our study was to 1) investigate extracellular electrograms in the AV junctional area in patients with AV node reentrant tachycardia during cardiac surgery; 2) compare the characteristics of these electrograms with those obtained in isolated porcine hearts; 3) explore the manifestation of multiple pathways; and 4) determine the origin of electrograms with slow deflections by correlating extracellular and intracellular recordings.

Methods

Multichannel extracellular recordings. Mapping of the electrical activity of the AV junctional area was carried out in 12 patients who underwent curative surgery for AV node reentrant tachycardia and 19 Langendorff-perfused porcine hearts.

Patients. Twelve patients (nine women and three men, aged 18 to 60 years [mean 46]) were referred for surgical

therapy after three different drugs failed to suppress the tachycardia. In all patients, paroxysmal AV node reentrant tachycardia was diagnosed by standard electrophysiologic criteria (14). One week before surgery, antiarrhythmic medication was discontinued. In 10 patients, common AV node reentry (14) was demonstrated, whereas the uncommon type was observed in the remaining 2 patients. With the patient on cardiopulmonary bypass, the right atrium was opened by a long oblique incision to expose the AV junctional area. Two bipolar hook electrodes—one attached to the right atrium, the other to the right ventricle—served as reference electrodes. Stimulation was performed through bipolar hook electrodes—one on the right atrium, the other on the right ventricle. Mapping was carried out under normothermic perfusion.

Pigs. Pigs weighing between 15 and 20 kg were anesthetized with sodium pentobarbital (30 mg/kg body weight). After thoracotomy, the heart was rapidly removed and connected to a Langendorff perfusion setup as described previously (15). An incision was made in the right atrium, from the vena cava anterior to the vena cava posterior, and extended toward the atrial appendage. Reference signals were recorded with two small bipolar hook electrodes attached to the septum of the right atrium and to a convenient site on the right ventricle. A similar electrode was used for stimulation and was attached near the ostium of the coronary sinus. The junctional area was scanned with a hand-held probe (bipolar recording, poles 2 mm apart) to locate the site with the largest His deflection. This site was marked with a fine needle (diameter 300 μm) that did not influence AV conduction in any way. Basic stimulation was performed with a cycle length just below that of the spontaneous rhythm.

Mapping techniques. Electrograms were recorded with a rod electrode harboring 64 terminals—the cut ends of stainless steel wires (diameter 70 μm)—on its tip. The wires were cut at the same level and arranged in an 8 × 8 matrix at interelectrode distances of 1 mm. An additional wire, cut 1 mm shorter than the others, was located in the middle of the matrix and served as the indifferent pole. In this way, 64 semiunipolar recordings were obtained, thus combining the advantages of a unipolar and a bipolar lead.

A data acquisition system enabled the simultaneous recording of the 64 signals. These were bandpass filtered (low cutoff 3 dB point 1 Hz, high cutoff 3 dB point 1 kHz) and amplified 200 times. Peak to peak noise level of the amplifiers was 40 μV; the sample frequency was 1 kHz.

In patients, the rod electrode was positioned by hand at one or more sites along the attachment of the tricuspid valve between the membranous septum and the ostium of the coronary sinus. For measurements in the pig hearts, the rod was mounted in a micromanipulator and positioned parallel to the annulus fibrosus at one or more sites between the marked location of the His bundle and the ostium of the coronary sinus.

Criteria for AV node deflections. Simultaneous recordings with intracellular and extracellular electrodes have shown that some of the deflections found in extracellular signals recorded from the AV junctional area represent activation in the AV node (10). Our observations showed that extracellular signals recorded from the AV junctional area between the His bundle and the coronary sinus consist of at least two components. The first component usually comprises one or more sharp deflections originating from activation of atrial tissue. A second deflection, which is always present, mirrors remote activation of the ventricle. Ventricular deflections were always synchronous and had a similar configuration independent of the recording site.

In several recordings, a third component was present, sandwiched between the atrial and ventricular deflections (Fig. 1). These components usually having slow downstrokes (slow potentials) resembled the AV node deflections recorded by other investigators (10). Deflections in Figure 1 that are caused by atrial activation are marked by A in the upper tracing, whereas deflections marked by V express remote activation of the ventricle. Between these components, a third is present (marked AV). The upper panels show spread of activation of the atrial and AV node components.

Because several other explanations could account for the AV components (16), a validating procedure was required to confirm the AV node origin of these deflections. We considered complexes occurring between the atrial and ventricular components as originating from the AV node if they met the following criteria. 1) Spread of activation of the complexes was <0.1 m/s (17). The time of steepest negative deflection was used to determine activation time (10). 2) The complexes were recorded from at least 10 clustered sites. This requirement was introduced because spread of activation can be determined reliably only if signals are recorded from contiguous sites. 3) The maximal negative derivative of the complexes was >−0.2 V/s. This cutoff value was chosen on the basis of the steepness of distinct atrial deflections (amplitude >1 mV), which was always more negative than −0.2 V/s.

Intracellular recordings. In five porcine hearts extracellular and intracellular recordings were made simultaneously from sites revealing slow potentials similar to the AV node complexes in the multichannel recordings. Hearts were Langendorff perfused as described before, but diacetylmonoxime was added to the perfusion fluid to abolish contraction (18). The extracellular electrode consisted of a silver wire (diameter 0.2 mm), isolated except at the tip, which was coated with a silver chloride layer. Recordings were made with respect to the cavity potential of the left ventricle. Intracellular recordings were made with conventional microelectrodes.

Histologic investigation. Histologic investigation was performed on four pig hearts, using standard techniques after fixation with formalin. Sections of 5 to 10 μm thickness were analyzed from sites at which microelectrode impalements were made. At these sites, extracellular recordings showed
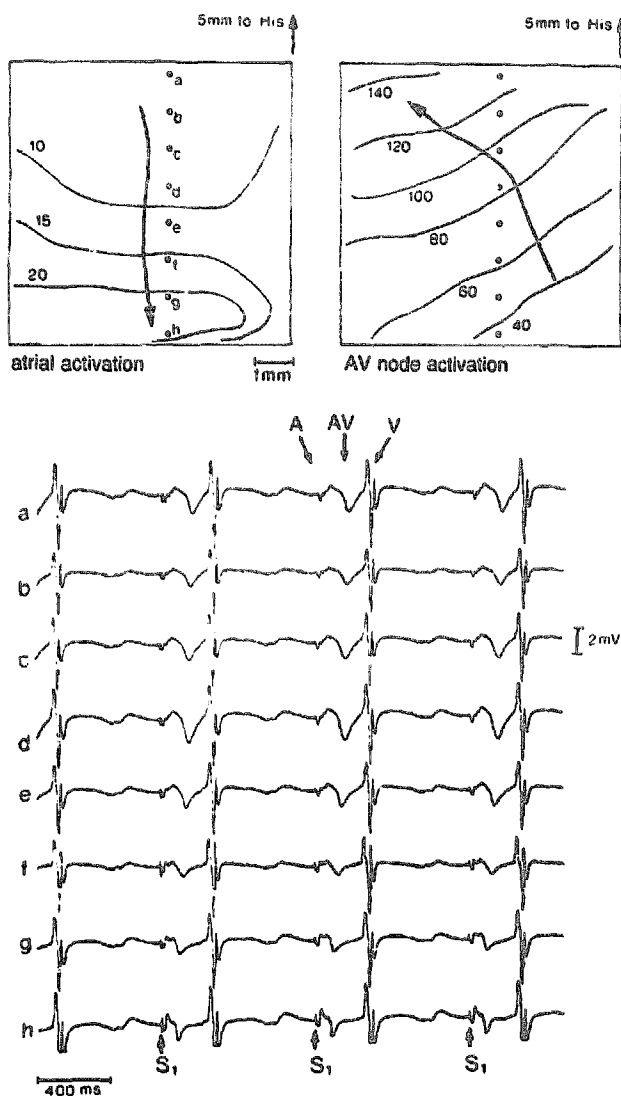
Figure 1. Upper panels, Atrial and atrioventricular (AV) node activation patterns of the AV junctional area of a porcine heart during atrial stimulation. Arrows indicate the main spread of activation. The right border of the recording area was parallel to the annulus fibrosis; the upper right corner was located 5 mm from the His bundle. Signals that were used to construct the activation patterns were recorded simultaneously from 64 sites at 1-mm interelectrode distance. Atrioventricular node signals were recorded from 58 sites. Lower panel, Extracellular electrograms are recorded at the sites indicated in the upper panels. The signals exhibit three components. Components marked A in the upper tracing were generated by activation in atrial tissue; V points to the remote components of ventricular depolarization. Deflections marked AV between the atrial and ventricular components mirror the activity of subendocardial layers of the AV node. S_1 = basic stimulus.

slow potentials. The plane of sectioning was always perpendicular to the AV ring. Sections were stained alternately with Masson trichome and hematoxylin-eosin.

Results

Multichannel extracellular recordings. Electrograms from the AV junctional area and fulfilling the criteria for classifi-

cation as AV node in origin during sinus rhythm or atrial stimulation, or both, were recorded in five human (41.6%) and eight porcine (42.1%) hearts. Of these, two human and three porcine hearts manifested AV node signals during ventricular stimulation as well.

Characteristics of AV node complexes. The amplitude of the signals that fulfilled the criteria of an AV node origin ranged from 0.1 to 3 mV (mean 0.8 mV). The maximal negative derivative ranged from -0.01 to -0.2 V/s (mean -0.06 in porcine and -0.12 in human hearts). The amplitude of the preceding atrial complexes was on average 1.25 mV in porcine hearts and 0.88 in human hearts. In areas deprived of AV node potentials, atrial signals could be as high as 15 mV. Their maximal negative derivative had a mean value of -3.3 and -1.4 V/s for porcine and human hearts, respectively. In four hearts, a gradual transition was observed from sharp deflections (dV/dt < -0.2 V/s) to slow AV node complexes. In three of these hearts, the signals exhibiting the sharpest deflections we e recorded at sites located posterior to those where signals had a slow downstroke. In one heart, the sharper deflections were recorded close to the bundle of His. Characteristics of AV node signals recorded in the human hearts did not differ significantly from those in the porcine hearts.

Spread of AV node activation. *Sinus rhythm and basic atrial stimulation.* In five human and eight porcine hearts, AV node signals were recorded from 10 to 45 clustered sites during either sinus rhythm or atrial stimulation. This made a tentative description of the spread of activation possible. In one human heart, spread of AV node activation of two successive sinus beats was dissimilar, although the PR interval and the configuration of the P wave on the surface leads I, II and III were identical. Figure 2 illustrates these two beats. The AV node deflections (marked AV in the upper tracings) recorded from the same site for the two successive complexes differ in configuration and time of occurrence. The latter is expressed by the difference in pattern of AV node activation (upper panels). Spread of atrial activation in the AV junctional area was similar for both complexes.

In the remaining four human and in all porcine hearts in which AV node signals were recorded during anterograde conduction, the activation pattern was identical for sinus and stimulated beats (basic cycle length ranging from 400 to 800 ms).

Premature atrial stimulation. In five porcine hearts with AV node deflections during basic atrial stimulation, a premature stimulus was delivered after every eighth basic stimulus. In none of these hearts did premature stimulation result in echo beats that reexcited the atria. In three of the five hearts, the AV node activation patterns evoked by basic and premature stimuli were dissimilar. In two of these, multiple AV node deflections were evoked by premature stimuli. The activation maps showed two consecutive wave fronts crossing the same area in opposite direction. An example is shown in Figure 3. During basic stimulation of the
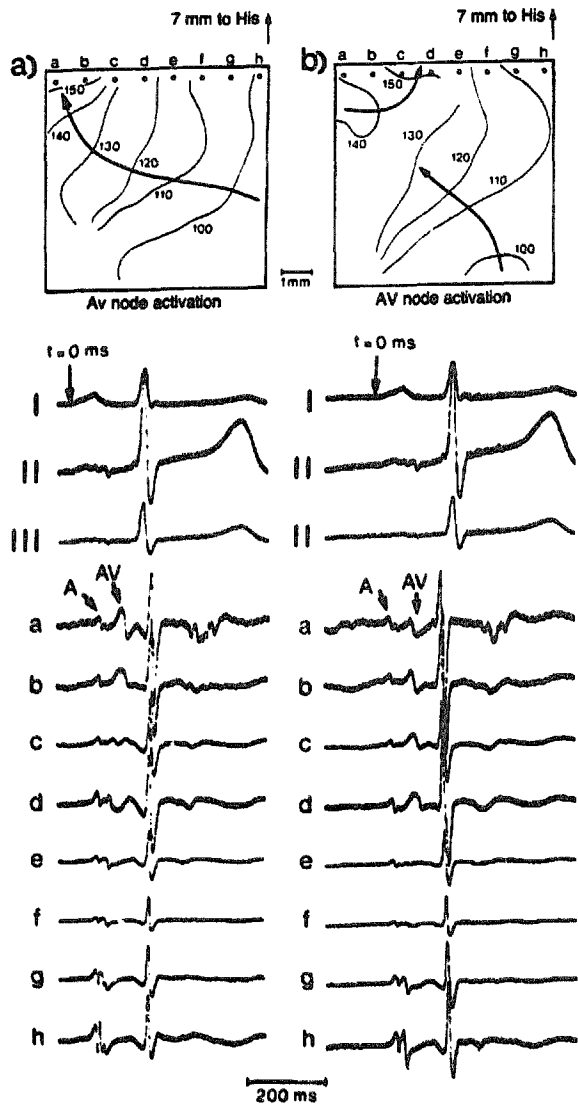
Figure 2. Upper panels, Atrioventricular (AV) node activation patterns of two successive beats during sinus rhythm in a patient operated on for recurrent AV junctional reentrant tachycardia. The right border of the recording area was parallel to the annulus fibrosis; the upper right corner was located 7 mm from the His bundle. Isochrones are 10 ms apart and are timed with respect to the onset of atrial activation (t = 0 ms in lead I). Arrows indicate the main spread of activation. Lower panels, Signals are the surface leads I, II and III and the extracellular electrograms that were recorded at the sites indicated in the activation patterns. Atrial components are marked by A, the AV node component by AV in tracings a. The AV node components are followed by remote ventricular deflections. Atrioventricular node deflections were recorded from 60 sites.
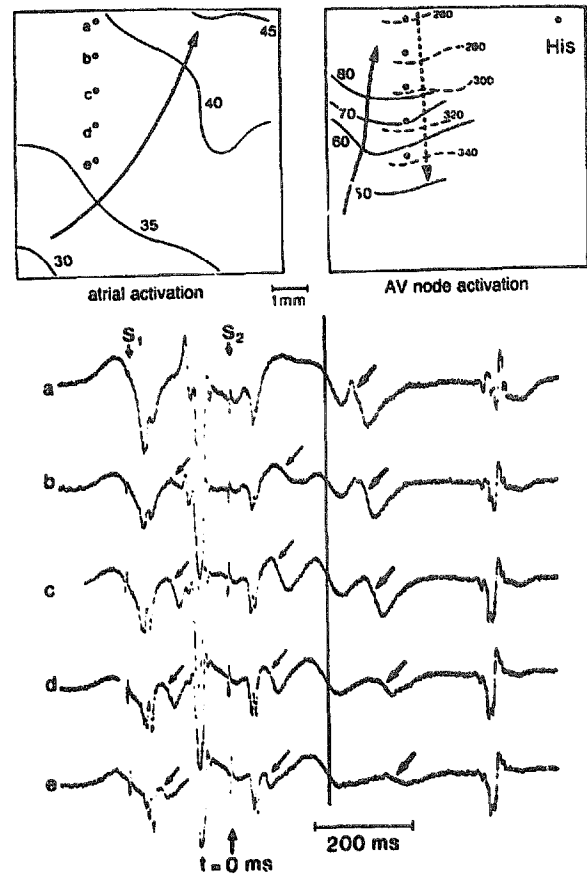

Figure 3. Upper panels, Atrial and atrioventricular (AV) node activation patterns during premature atrial stimulation in a porcine heart. The right border of the recording area was parallel to the annulus fibrosis; the upper right corner was located at the position of the His bundle. The AV node activation shows two patterns (solid lines 50 to 80 ms and dashed lines 260 to 340 ms). The main spread of activation is indicated by arrows and shows that spread of the two wave fronts takes place in opposite directions. Lower panel, Extracellular electrograms recorded at sites indicated in the upper left panel. The last basic stimulus (basic cycle length 600 ms) is indicated by S_1. The arrows in tracings b to e to the right of S_1 point to deflections from the AV node. After each eighth basic stimulus, a premature stimulus (S_2) was delivered. This stimulus induced atrial activation that failed to conduct to the ventricle. As was the case during basic stimulation, atrial activation caused by the premature stimulus invaded the AV node (small arrows to the right of S_2). During atrial activation, however, the AV node generated a second component (bold arrows). The deflections along the vertical line represent repolarization of the ventricle and occur simultaneously in all signals. During basic stimulation, AV node complexes were recorded at 20 sites and during premature beats at 18 sites.

atrium (S_1), AV node deflections were demonstrated at several recording sites (small arrows in tracings b to e between S_1 and S_2). After the premature stimulus (S_2), similar deflections were observed in the same tracings (small arrows in tracings b to e, following S_2). The isochronic pattern derived from these deflections is indicated by the solid lines in the upper right panel. This activation pattern is similar to that occurring after application of an extrastimulus

that generated activation that only just conducted to the ventricle. After repolarization of the ventricle, other AV node deflections were recorded (bold arrows). The upper right panel shows the corresponding isochrones, indicated by broken lines. Spread of activation derived from this group of isochrones (dashed arrow) is opposite in direction to that seen in the first group (bold arrow). This wave front, which can be considered as an echo beat that failed to reexcite the atria, occurred when premature stimuli were applied with

Figure 4. Intracellular and extracellular recordings made during premature atrial stimulation. The atrium was stimulated from a septal site. The upper tracing (atrium) is a reference signal recorded from the right atrial appendage. Vertical lines are stimulus artifacts. The second tracing (extracellular) is a unipolar recording exhibiting slow potentials (open arrow). This recording was made at a site near the orifice of the coronary sinus. The third tracing (ventricle) is from a site on the right ventricular septum. Activation of the right bundle can readily be seen as a small spike (arrow). The fourth tracing is an intracellular recording made from a site close to that of the extracellular electrode. The downstroke of the slow potential coincides with the upstroke of the action potential, which has a slow upstroke velocity. Amplitude and upstroke velocity decrease after premature stimuli.
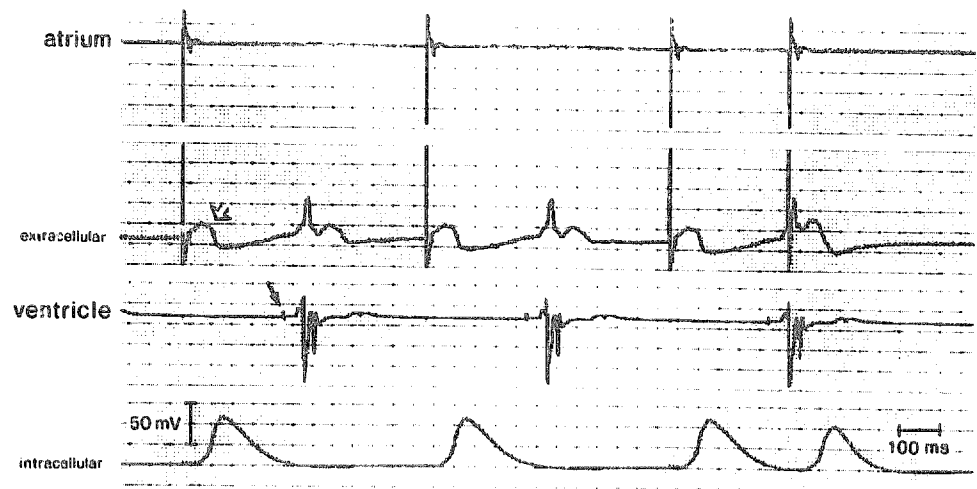
coupling intervals between 193 and 213 ms. The wave front was absent at longer as well as shorter intervals.

Spread of AV node activation after ventricular stimulation. In two human and three porcine hearts in which AV node signals were detected during sinus rhythm or atrial stimulation, or both, AV node complexes were recorded during ventricular stimulation as well. In three of these hearts, the complexes occurred after the atrial components. In one heart, multiple AV node complexes in the same recording were observed during basic ventricular stimulation, whereas only one complex was seen after premature stimuli. Premature beats that just failed to conduct to the atria were always followed by AV node deflections.

Intracellular recordings. In four of five porcine hearts slow potentials similar to the AV node signals were recorded from 1 to 8 sites (in total 14 sites) with a single extracellular electrode. Intracellular recordings from these sites were obtained during superficial impalement and invariably showed action potentials with slow upstrokes. At 10 recording sites, the upstroke coincided with the downstroke of the slow potential. At four sites, the upstroke was located between the preceding atrial electrogram and the negative slope of the slow potential. Time of activation was between 20% to 80% of the atrium–His bundle interval in all recordings.

During intracellular recordings at four sites, extrastimuli were applied and showed that the upstroke velocity and amplitude of the action potentials decreased at shorter coupling intervals. An example is illustrated in Figure 4. The intracellular recording was made from a site close to the orifice of the coronary sinus.

Histologic investigations. From the four hearts in which slow potentials were recorded, serial sections were taken

from six sites of microelectrode impalement. Upstroke of the action potentials at these sites coincided with the downstroke of the slow potentials recorded at the same site. Transitional cells running parallel to the endocardium were observed directly underneath the endocardium at all sites irrespective of the distance between the recording site and the compact node.

Transitional cells differ from working atrial cells in having a smaller diameter and reduced cross-striation (19). They are often widely separated and tend to be arranged individually, being interspersed with connective tissue. In our preparations, transitional cells could be readily distinguished on the basis of these properties.

Conclusions. Multichannel mapping shows that slow potentials can be recorded in about 40% of human as well as porcine hearts. During sinus rhythm, spread of activation corresponding to these slow potentials can occur by several paths without affecting the PQ interval. Spread of activation during premature stimulation often differs from that of basic beats. Multiple pathways were observed after atrial and ventricular stimulation. In several cases, slow potentials followed atrial deflections during retrograde conduction.

Intracellular recordings show that slow potentials are caused by cells with AV node characteristics. Depth and location of impalements, together with activation time and histologic analysis, strongly suggest that slow potentials arise in subendocardially located transitional cells overlying the compact node or posterior to it.

Discussion

The origin of extracellular electrograms. Extracellular recordings of the AV junctional area have been carried out in

experimental settings (10-13), as well as during clinical studies (8,9,16). Although the AV node seems the obvious source of deflections occurring between the atrial and ventricular components in extracellular recordings, several other explanations can be given for their origin: 1) injury caused by pressure or impalement of the electrodes, 2) activation of specialized atrial tissue, 3) ringing of filters, and 4) repolarization of atrial tissue (16).

For this reason, validating procedures must be performed to confirm the AV node origin of the observed extracellular complexes. In our study, it was stipulated that spread of AV node activation must be less rapid than that of atrial activation (<0.1 m/s). This requirement excludes deflections caused by either repolarization or injury of atrial myocardium because such signals will occur simultaneously. Moreover, injury was unlikely because of negligible pressure exerted by the multiterminal electrode as a result of its "large" total area. When positioned on ventricular myocardium or on the AV junctional area, the electrode did not cause lesion potentials. The characteristics of the intracellular complexes provided additional support for the AV node origin of the slow potentials.

A question to be addressed is whether slow potentials arise from activation in either transitional cells or cells of the compact node. Decreases in amplitude and upstroke velocity of the action potentials during premature stimulation suggest that they arise in N cells located in or close to the compact node (20). However, this may not be so because 1) the classification of AV junctional cells into AN, N and NH types (20,21) was derived from observations made in rabbit hearts. This classification may not be applicable in human or porcine hearts and is not strict because AN cells can have the characteristics of N cells (20). 2) Double components, which occur in recordings from N cells during premature stimulation (20), were not observed. 3) All action potentials with AV node characteristics were recorded during superficial impalement. 4) Depolarization of impaled cells always occurred within 20% to 80% of the atrial-His bundle interval, which is characteristic of AN cells (22). 5) Some recording sites were located near the orifice of the coronary sinus, far from the compact node. 6) The compact node comprises only a small zone of the order of 1 or 2 mm^2 at the middle of the junctional area (20), which is not compatible with the widespread location of sites with slow potentials. 7) The shortest distance from the compact node to the site of recording was about 1 mm. The amplitude of an extracellular signal generated by activation through a bundle rapidly decreases with distance (23). The recorded voltage is also reduced because nodal cells in the compact node are intermingled with fibrous tissue (19). 8) Sites from which AV node deflections with a large amplitude were recorded sometimes bordered sites where no AV node deflections were found. This observation is not compatible with the view that signals represent distant activation of the compact node, but it is compatible with the concept that activation in

the transitional cells accounts for the extracellular deflections.

Relation between slow potentials and AV conduction. The fact that AV node conduction of consecutive sinus beats can differ (Fig. 2) while the PR interval is unchanged suggests that activation also occurred by other, not observed, AV node pathways. This is conceivable because input to the compact node occurs through three groups of transitional cells, one of which is located in deeper layers (19). Therefore, we are aware of not having recorded the activation of all transitional cells. In addition, AV node signals may be due to activation in dead-end pathways that have been demonstrated in the AV junctional area (24). This can explain our observation that slow potentials arise after atrial deflections during retrograde conduction.

Haissaguerre et al. (9) described the recording of slow potentials in the perinodal region in patients with AV node tachycardia. They recorded these potentials from the mid and posterior septum, anterior to the ostium of the coronary sinus. These slow potentials have several features in common with the AV node signals of our recordings. 1) Sharp potentials were recorded from a smaller number of sites than were slow potentials. 2) The configuration of the signals could vary during sinus rhythm in the same patient. 3) At high stimulation rates, the signals decreased in amplitude. 4) The signals were recorded at contiguous sites anterior to the coronary sinus. In addition, Haissaguerre et al. (9) also recorded slow potentials in a control group of patients who were found to have no AV node tachycardia. This finding is compatible with our observation of AV node signals in the porcine hearts, suggesting that the potentials are a common phenomenon in the AV junctional area of mammalian hearts. The main discrepancy between our observations and those of Haissaguerre et al. (9) concerns the number of patients in whom the signals were recorded. They recorded slow potentials in virtually all patients, whereas we could record them in only 42% of the hearts. The origin of this discrepancy may be a difference in the input noise level of the amplifiers or the stringent requirements of clustered sites from which AV node signals had to be recorded in our study.

Jackman et al. (8) reported the recording of sharp potentials posterior to the AV node near or in the ostium of the coronary sinus. They suggested that these signals represent activation of the atrial end of the slow pathway. The slow pathway potentials are described as being sharper and of greater magnitude than the local atrial signals. We recorded sharp deflections that were probably related to contiguous AV node deflections in four hearts. In three of these, the slope of the signals decreased with increasing distance to the preceding atrial deflection; the slope then gradually faded into the AV node deflections that were recorded farther away from the ostium of the coronary sinus. This phenomenon is comparable with the findings of Spach et al. (10), who showed that the transition from atrial myocardial fibers to transitional cells is gradual rather than abrupt. Although it is conceivable that the signals with sharp deflections repre-

sent the slow pathway potentials recorded by Jackman et al. (8), our signals were recorded anterior to the ostium of the coronary sinus, a recording site different from that used by Jackman et al. (8). In addition, the amplitudes of the sharp potentials in our study did not vary as much as those in the recordings by Jackman et al. (8).

Limitations of the extracellular recording technique. Why were slow potentials recorded in only 42% of the hearts during multichannel mapping but recorded from at least one site in four of five hearts during the microelectrode studies? The answer may lie in the following considerations: 1) the spatial resolution of a roving probe is virtually unlimited; 2) activation in transitional cells can be masked by activation in overlying atrial muscle; 3) recording of slow potentials can be missed, either because they are too small or because activation runs through deeper layers of transitional cells; and 4) the prerequisite of 10 clustered sites from which AV node deflections had to be recorded during mapping is conservative, implying that we could have missed recording AV node signals from solitary sites.

Although the results of simultaneous recordings of intracellular and extracellular signals strongly support the concept of the slow potentials originating in transitional cells, further investigation is necessary to clarify the importance of these signals for AV conduction and AV node tachycardia.

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