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Anisotropic Conduction in the Triangle of Koch of Mammalian Hearts: Electrophysiologic and Anatomic Correlations

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Objectives. **The purpose of this study was to characterize anisotropy in the triangle of Koch by relating electrophysiology with anatomy.**

Background. **Atrioventricular (AV) node fast and slow pathway characteristics have been suggested to be due to nonuniform anisotropy in the triangle of Koch.**

Methods. **During atrial pacing, we determined the electrical activity within the triangle of Koch by multichannel mapping in 11 isolated hearts from pigs and dogs. Orientation of fibers was determined in nine hearts.**

Results. **Fibers were parallel to the tricuspid valve annulus (TVA) in the posterior part of the triangle of Koch. In the midjunctional area, the direction of the fibers changed to an orientation perpendicular to the TVA. During stimulation from posterior and anterior sites, activation proceeded parallel to the TVA at a high conduction velocity (0.5 to 0.6 m/s). During stimulation from sites near the coronary sinus, a *narrow* zone of slow conduction occurred in the posterior part of the triangle of Koch where activation proceeded perpendicular to the fiber orientation. Above and below this zone, conduction was fast and parallel to the annulus. After premature stimulation, conduction delay in the triangle of Koch increased by 4 to 21 ms; in contrast, the AH interval increased by 80 to 210 ms.**

Conclusions. **Data support the concept of anisotropic conduction in the triangle of Koch. Activation maps correlated well with the arrangement of superficial atrial fibers. Comparison of conduction delay in the triangle of Koch and AH delay after premature stimulation disproves that anisotropy in the superficial layers plays an important role in slow AV conduction.**

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Anisotropic conduction refers to differences in the velocity of conduction related to the direction of propagation relative to the orientation of muscle fibers. Conduction perpendicular to the alignment of the fibers is slower than conduction in the longitudinal direction (1–4). Such properties of anisotropic conduction in cardiac muscle may be responsible both for slow conduction and for unidirectional conduction block, which may permit reentry (5,6).

Spach and Josephson (6) suggested that the transitional zone of the atrioventricular (AV) junctional area has marked nonuniform anisotropic properties and therefore could provide a mechanism for the slow and fast pathway characteristics of the AV junction. During atrial stimulation in the anterior part of the AV node area, they observed a high velocity of conduction (0.39 m/s) parallel to the tricuspid valve annulus (TVA) along with large biphasic extracellular electrograms. In contrast, when the site of stimulation was in the floor of the coronary sinus, activation was propagating toward the annulus at a much lower speed (0.07 m/s). In the latter setting, electrograms showed multiple deflections typical of slow transverse conduction in nonuniform anisotropic tissue. These observations are in keeping with an anatomic study (7) showing that the fibers in the posterior approach to the AV node of the rabbit were oriented parallel to the TVA. These fibers were small and formed irregular bundles separated by connective tissue. As far as we are aware, however, direct anatomic-electrophysiologic correlations have not been performed.

The objectives of this study were 1) to identify the anisotropic electrical properties of the AV junctional area, 2) to correlate the anisotropic electrical properties with the underlying anatomy, and 3) to relate the increase in activation delay in the superficial layers during premature stimulation to the increase in the AH interval.

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Abbreviations and Acronyms

AV = atrioventricular
CS = coronary sinus
DAM = diacetyl monoxime
HRA = high right atrium
IM = intramuscularly
OF = oval fossa
TVA = tricuspid valve annulus

Methods

Studies were performed in isolated, blood-perfused porcine and canine hearts. A multiterminal electrode was used to map the electrical activity within the triangle of Koch. Diacetyl monoxime (DAM) was added to the perfusate to dampen cardiac contractions. The heart was paced from several sites to change the direction of activation. The position of the mapping electrode was marked after completion of the electrical studies, and anatomic studies were performed to reveal the orientation of the superficial fibers.

Preparation of the hearts. Nine New Yorkshire pigs (6 to 8 weeks old, weight 15 to 25 kg) and two mongrel dogs (weight 20 to 30 kg) were investigated. Animals were premedicated with azaperon (12 mg/kg body weight intramuscularly [IM]), ketamine (15 mg/kg IM) and atropine (0.5 mg/kg IM), then anesthetized with sodium pentobarbital (35 mg/kg intravenously).

Hearts were excised, cannulated to a Langendorff perfusion setup and perfused with a blood-Tyrode mixture as described before (8).

A Y-shaped incision was made, running from the orifice of the inferior to the superior cava vein and into the right atrial appendage to expose the triangle of Koch and its surrounding area. The sinus node was resected to avoid interference from sinus rhythm during pacing.

Recording techniques. Bipolar hook electrodes used for extracellular recordings were placed in the right atrium (for reference purposes) and over the His bundle to determine AH conduction. To avoid artifacts due to vigorous cardiac contractions, 1 to 1.5 g of DAM was added to the perfusate. The effects of DAM on the electrophysiologic properties were not significant (9,10).

Mapping of the electrical activity was done with a multiterminal electrode that was adapted to the curvature of the triangle of Koch. The mapping electrode contained 96 quasiunipolar terminals, each consisting of a recording and a reference electrode, embedded in a two-component resin (Palapress). Recording and reference electrodes consisted of silver wires (diameter 100 μm). The recording electrodes were cut at the same level and arranged in a 12 $\times$ 8 matrix at interelectrode distances of 1 mm. The reference electrodes were cut 1.5 mm shorter and positioned close to the recording electrodes. The reference electrodes were not in contact with the tissue, although they were submerged in a layer of fluid overlying the endocardium. In this way, 96 quasiunipolar recordings were obtained, combining the advantages of bipolar and unipolar recordings (11,12). Remote signals were attenuated and unipolar characteristics were preserved. As in unipolar electrograms, the local activation time is represented by the time of the maximal negative derivative of the signal (13). The mapping electrode was mounted in a micromanipulator for accurate positioning over the triangle of Koch. The right margin of the electrode was positioned close to the His bundle electrode.

Signals were amplified 256-fold. The lower and upper cutoff frequencies of the amplifiers were 0.1 and 500 Hz, respectively. A system for acquisition of data allowed simultaneous recording of the 96 signals at a sample frequency of 1 kHz. Signals were stored on a hard disk of an IBM-compatible computer system.

Analysis of the electrical activation. The activation times of all deflections within the electrograms were determined. The time of the deflection with the most negative value of the first derivative was selected by the computer and used as the local activation time. The latter could be corrected by the operator in case of artifacts. The activation times of the 96 electrograms were used to construct isochronal maps. The apparent conduction velocity was obtained by dividing the distance between two electrode terminals by the difference in the time of local activation at these sites of recording. Isochronal lines had to be perpendicular to the line connecting the two recording sites. Slow conduction was defined as a velocity of $<$0.1 m/s.

Stimulation protocol. Bipolar electrodes, consisting of two silver wires (diameter 0.2 mm, interelectrode distance 0.5 mm) were used for stimulation. For mapping of the electrical activity, stimuli of 2 ms duration and 1.5 to 2 times diastolic threshold were applied at cycle lengths of 600 ms. In four hearts, stimulation was performed from the oval fossa (OF), from the high right atrium (HRA) and from 18 sites around the margins of the electrode. Premature stimulation at the latter sites was also carried out in these hearts. In the seven other hearts, we stimulated from the fossa, the high right atrium and from a posterior and an anterior site within the triangle. Anterograde and retrograde conduction curves were determined for all hearts.

Effects of DAM. To assess the effects of DAM, we determined the AH interval, the anterograde refractory period, and the Wenckebach point before and after DAM administration in six hearts.

Anatomic studies. Studies were performed in seven porcine and two canine hearts after the electrophysiologic study was completed. All hearts were preserved in a 10% formaldehyde solution and then transferred to the National Heart & Lung Institute, London for anatomic analysis. Pins were placed at the edges of the mapping electrode to mark its position. The endocardium was peeled off without damaging the myocardial fibers. Watchmaker's forceps were used to follow the orientation of the fibers. Serial histologic sections were made from blocks delineated by the marker pins on two porcine and two canine hearts.

Statistics. Values are expressed as mean ± SEM. The effects of DAM were assessed by using the paired *t* test.

Results

Experimental preparation. Stable AV conduction (changes in the AH interval <10%) was maintained throughout the experiments. After excision of the sinus node, an AV junctional or a ventricular escape rhythm ensued. After DAM was added to the perfusate, the electrode was positioned and mapping was performed. DAM did not cause significant changes in AH intervals, refractory periods or the Wenckebach point (mean ± SD) AH interval before DAM 69 ± 11 vs. 71 ± 11 ms after DAM; atrial effective refractory period 150 ± 16 vs. 147 ± 16 ms; AV node effective refractory period 161 ± 20 vs. 157 ± 20 ms; Wenckebach point 208 ± 13 vs. 203 ± 8.

Anatomic examination. Serial histologic sections confirmed the orientation of the superficial fibers as shown by gross dissection in both porcine and canine hearts. These superficial fibers did not show histologically specialized characteristics and resembled ordinary atrial fibers. In the node region, they represented the atrial overlay fibers and varied from 10 to 30 cells deep. Figures 1 and 2 show two kinds of geometric patterns of the myocardial fibers in and near the triangle of Koch. Both patterns were found in dog as well as pig hearts. Figure 1A is a photograph illustrating the fiber orientation in one of the pig hearts and Figure 1B is a schematic drawing of this photograph, highlighting the main pattern of the fibers (b).

As illustrated in Figure 1B, fibers in the posterior region (a), between the coronary sinus (CS) ostium and the tricuspid valve annulus, ran parallel to the TVA. Toward the anterior region (b), the fibers turned off in the direction of the interatrial septum to proceed finally almost perpendicular to the TVA. Fibers in the far anterior region (c) were, again, more or less parallel to the TVA and contacted the fibers arriving from the TVA under a sharp angle. In fact, the fibers from the anterior region (c) ran underneath the perpendicular fibers (b).

Figure 2, A and B, shows the course of the fibers in a dog heart. The fibers in the posterior region also ran parallel to the TVA. In the anterior area the course of the fibers was perpendicular to the TVA, but, in contrast to the pattern shown in Figure 1, they seemed not to be in continuation with the fibers approaching from the posterior area.

Isochronal maps. Figure 3, B to F, shows activation patterns in the same heart as in Figure 1 after stimulation from five sites located along the margins of the recording electrode. The pattern of activation depended strongly on the site of stimulation. Pacing from either anterior or posterior sites gave rise to activation with widely separated isochronal lines, indicating fast conduction (mean conduction velocity 0.5 to 0.6 m/s) parallel to the TVA. Crowding of isochronal lines arose when stimulation was performed from sites along the upper margin of the recording electrode.

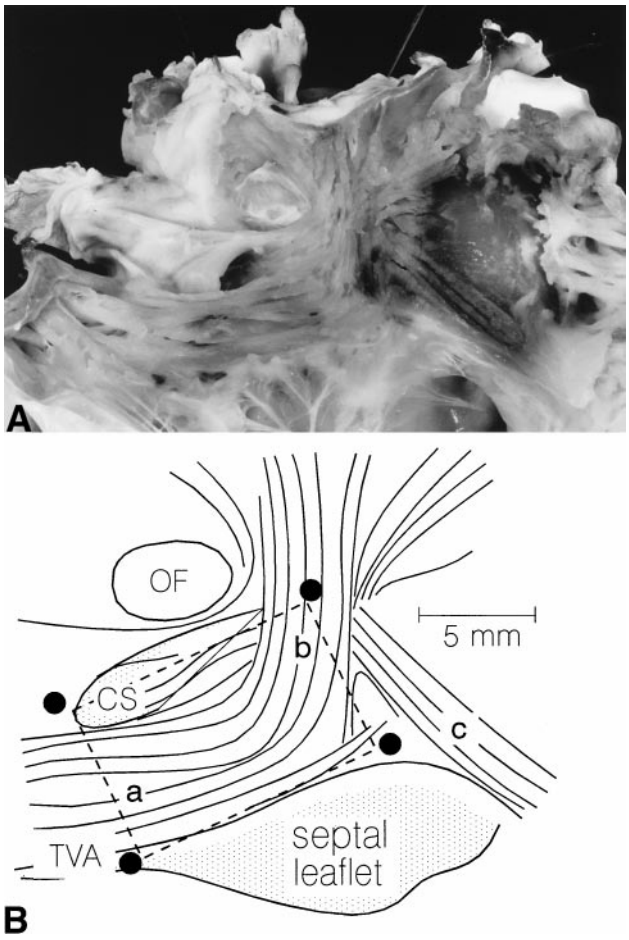

Figure 1. A, Photograph of the junctional area of a porcine heart, showing the geometric pattern of the myocardial fibers in and near the triangle of Koch. **B,** Schematic drawing of the photograph, highlighting the main pattern of the fiber direction. The **four circles** and the **dashed rectangle** mark the position of the recording electrode. a = posterior region; b = anterior region; c = far anterior region. See text for discussion.

Stimulation from the right margin of the recording area. Figure 3B shows the activation pattern after stimulation from site I, located in the anterior area, near the TVA. Isochronal lines were nearly perpendicular to the TVA, compatible with activation parallel to the direction of fibers. There were small differences in the distance between the isochronal lines, suggesting marginal differences in conduction velocity. The activation pattern changed only slightly when the stimulation electrode was moved along the right margin of the recording electrode. Even during stimulation from the upper right edge of the recording area (II), isochronal lines were more or less perpendicular to the TVA (panel C). Only near the TVA did the isochronal lines tend to become parallel to it.

Stimulation from the upper margin of the electrode. The activation pattern changed dramatically when the site of stimulation was moved to locations along the upper margin of the recording electrode. When stimulated from site III, a narrow and short zone of crowded isochrones was seen near

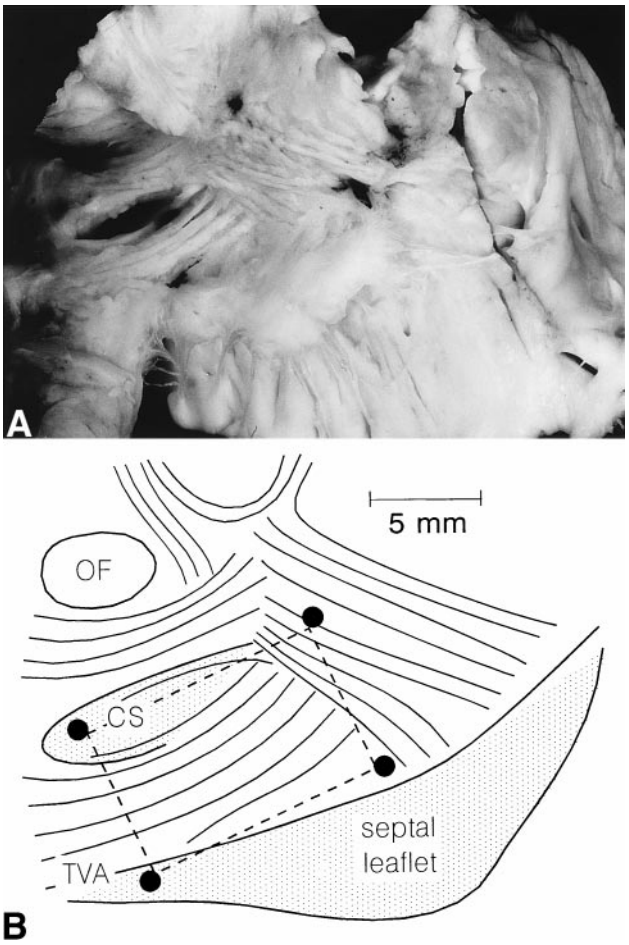

Figure 2. A, Photograph of the junctional area of a canine heart, showing the geometric pattern of the myocardial fibers in and near the triangle of Koch. **B,** Schematic drawing of the photograph, highlighting the main pattern of the fiber direction. Symbols as in Figure 1.

the upper margin of the recording area (Fig. 3D). This zone was almost parallel to the annulus. Crowding of isochrones, indicating a reduced conduction velocity, occurred because activation had to propagate perpendicular to the direction of the fibers in this area. In contrast to conventional patterns of activation in areas where propagation proceeds perpendicular to the alignment of fibers, this zone of crowded isochrones was narrow. In the right and lower part of the recording area, isochronal lines were further apart, indicating faster conduction. Here, activation seemed to follow the curvature of the fibers in the anterior area (b in Fig. 1B). Isochronal lines near the TVA tended to run perpendicular to the TVA, indicating that conduction was parallel to it. Another activation front parallel to the TVA arrived from the posterior region and collided with the first one, 2 mm away from the left margin of the electrode (26-ms isochronal line).

Stimulation from other sites along the upper margin, to the left of site III, resulted in similar activation. The zone of crowded isochrones remained narrow, but its length increased when the site of stimulation was moved to more posterior sites. The apparent speed of conduction in the area of crowded isochrones was as low as 0.08 m/s.

When stimulation was applied from the upper left edge of the recording electrode (IV), the zone of crowded isochrones extended to 7 mm (Fig. 3E). Close to the upper margin, activation ran rightward at an apparent speed of ~0.5 m/s. Near the right margin, activation again tended to follow the curvature of the fibers, resulting in activation running toward the TVA. Before this activation front could move posteriorly, however, it collided with another front arriving from the posterior region. The latter front proceeded parallel to the TVA at a speed of ~0.5 m/s.

Stimulation from the left margin of the recording area. When the site of stimulation was moved on to the left margin of the electrode, toward the TVA, the zone of slow conduction gradually disappeared. Stimulation from sites along the lower left margin of the electrode gave rise to activation patterns in which isochronal lines ran almost perpendicular to the TVA. In the anterior part of the recording area, isochronal lines were slightly crowded, suggesting reduced speed of conduction (0.25 m/s vs. 0.5 m/s in the posterior part, Fig. 3F). The reason for the crowding of the isochronal lines may be the change of the alignment of the fibers in the anterior part of the triangle. Crowding of isochrones in the anterior region became less pronounced when the site of stimulation approached the annulus.

Stimulation from the high right atrium. During stimulation from the high right atrium, activation maps revealed oblique isochronal lines that ran almost perpendicular to the TVA in the anterior region. Patterns were very similar to those obtained when stimulation was performed from the right upper edge of the recording area (Fig. 3C).

Stimulation from the oval fossa. Stimulation from this site resulted in patterns of activation very similar to those obtained when stimulation was done from the upper margin of the recording area (site III, Fig. 3D). Characteristic was the narrow zone of crowded isochrones in the posterior part of the triangle of Koch.

Stimulation from anterior and posterior sites. Such stimulation produced activation that was fast and parallel to the TVA. Isochronal patterns were compatible with those illustrated in Figure 3, B and F.

Stimulation from the orifice of the CS. A narrow zone of crowded isochronal lines that ran nearly parallel to the TVA was observed when the preparation was stimulated from inside the mouth of the coronary sinus (CS). At both sides of this zone, isochronal lines were more or less perpendicular to the direction of the fibers, similar to the pattern shown in Figure 3E.

AH interval after baseline and premature stimulation. During baseline stimulation, the delay between earliest and latest activation within the recording area ranged from 21 to 33 ms, depending on the site of stimulation. The largest delay occurred when stimulation was performed from sites along the upper margin of the recording electrode. In contrast, the AH interval usually had its smallest value when stimulation was

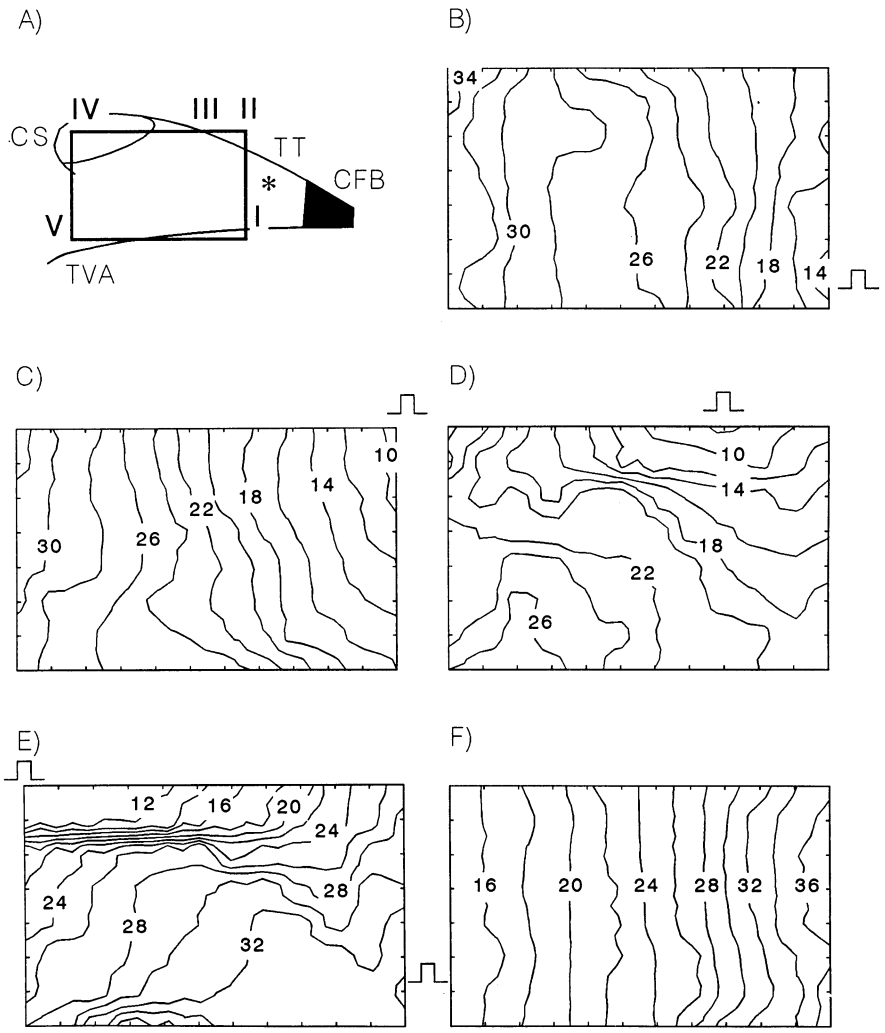

Figure 3. Activation maps during stimulation from five sites along the margins of the recording electrode. Maps were derived from electrograms recorded in the porcine heart of Figure 1. **A,** Schematic drawing of the triangle of Koch; the **rectangle** indicates the position of the electrode. Stimulation sites are indicated by I to V. **B** to **F,** Isochronal maps. **Numbers** are activation times in ms, measured with regard to the stimulus. Isochronal lines are drawn every 2 ms. The position of the stimulation electrode is indicated by **markers next to the maps.** The **asterisk** marks the position of the His electrode. See text for discussion. CFB = central fibrous body; TT = tendon of Todaro.

performed from the upper margin of the electrode array. Differences in the AH interval ranged from 3 to 10 ms when the site of stimulation was changed.

In four hearts, premature stimulation was achieved from all sites along the margin of the electrode. After premature stimulation at coupling intervals marginally longer than the AV node effective refractory period, major spread of activation was equal to that after baseline stimulation. Additional zones of conduction delay emerged or existing zones of delay became more pronounced.

After premature stimulation at coupling intervals that just caused conduction toward His, delay between earliest and latest activation within the recording area increased by 4 to 21 ms. In contrast, the AH interval increased by 80 to 210 ms after premature stimulation. As illustrated in Figure 4A, premature stimulation at a coupling interval that just caused conduction toward His resulted in an increase in the AH interval of 105 ms. Main spread of activation was equal to that after baseline stimulation (Fig. 4B). Despite the large increase in the AH interval, delay between earliest and latest endocardial activation within the recording area increased by only 4 ms (Fig. 4C).

Extracellular electrograms. Electrograms recorded during stimulation from sites along the left and right margins of the recording electrode usually showed a biphasic deflection, sometimes with minor fractionation (two deflections). Figure 5A illustrates electrograms recorded during stimulation from the left margin of the electrode. In contrast, fractionated electrograms occurred when the site of stimulation was moved to the upper margin of the electrode (Fig. 5B) or to the oval fossa.

Discussion

Our results show that the geometric array of the myocardial fibers in the triangle of Koch and its environs varies only slightly among hearts of dogs and pigs. The alignment of fibers in the posterior approach to Koch's triangle is parallel to the TVA, whereas the fibers run more perpendicular to the TVA in the anterior region. In most of the hearts studied, this change in the direction of fibers was smooth rather than

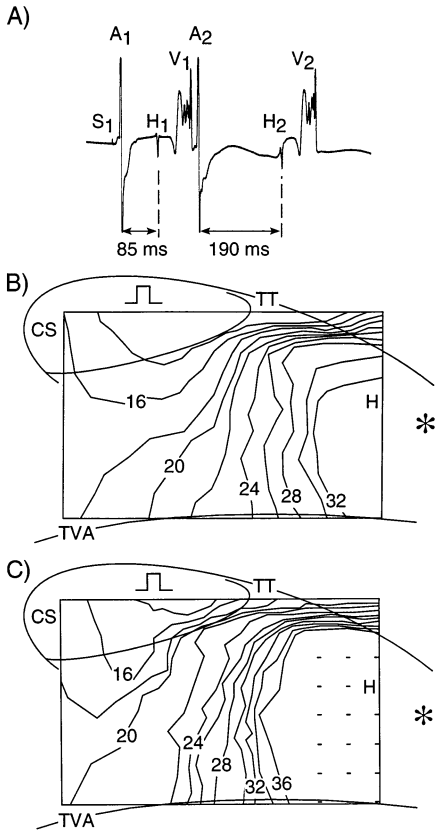

Figure 4. A, His bundle recording during basic stimulation at a cycle length of 600 ms and after premature stimulation with a coupling interval of 220 ms. **B** and **C,** Spread of endocardial activation in the triangle of Koch during baseline **(B)** and premature **(C)** stimulation. **Numbers** in the maps are activation times in ms measured with respect to the stimulus. Isochronal lines are drawn every 2 ms. The premature extrastimulus is masked by the ventricular electrogram (V_1). A_1, H_1 and V_1 = atrial, His bundle and ventricular deflections, respectively, during baseline stimulation; A_2, H_2 and V_2 = atrial, His bundle and ventricular deflections, respectively, after premature stimulation; H = terminal of the compound electrode, revealing a remote His deflection; S_1 = baseline stimulus; the **asterisk** marks the position of the His electrode; **dashes** indicate conduction block; other abbreviations as in Figure 3.

abrupt. In the most anterior region, the fibers were again seen running parallel to the annulus.

Patterns of activation correlated well with the course of the fibers. Stimulation from anterior and posterior sites, and from the high right atrium, resulted in rapid conduction parallel to the alignment of fibers. Stimulation from the OF and from sites near the orifice of the CS led to narrow zones of slow conduction in the posterior part of the triangle of Koch. Although activation was supposed to proceed perpendicular to the fiber direction during stimulation from sites near the orifice of the CS, spread of activation above and below the line of slow conduction was fast and parallel to the annulus, compatible with fast conduction parallel to the fibers.

Relation with the transitional cell zone. Histologic investigations (14) have shown that fibrous tissue, separating myocardial bundles, is abundantly present in the triangle of Koch. On the basis of histologic and electrophysiologic characteristics, cells in the triangle of Koch have been divided into three types, termed transitional, midnodal and lower nodal cells (7). In the rabbit, transitional cells constitute the most superficially located group of fibers. In the pig and dog, however, the superficial fibers, as in the human, are made up of cells that, histologically, are plain atrial myocardium (15). It is these fibers that were revealed by our dissection, with the posterior fibers running parallel to the TVA and the anterior fibers more or less perpendicular to it.

Nonuniform anisotropy. Spach et al. (1,3) have classified the anisotropic properties of cardiac muscle as uniform and nonuniform. Uniform anisotropy is characterized by wave fronts that are smooth in directions longitudinal as well as transverse to fiber orientation, indicating relatively tight coupling between fibers in all directions. Coupling, however, is tighter in the longitudinal than in the transverse direction, resulting in fast conduction parallel to the fibers and slow conduction perpendicular to their longitudinal alignment. Extracellular waveforms recorded during both longitudinal and transverse propagation are smooth with single deflections (16).

Anisotropy is said to be nonuniform when side to side electrical coupling of adjacent groups of parallel fibers is absent because of the interposition of strands of connective tissue (17). This connective tissue may be a normal component of the heart in regions such as the terminal crista, or can result from aging or pathologic changes. Propagation of activation transverse to the long axis is interrupted, such that adjacent bundles are excited in an irregular sequence which results in slow conduction. The irregular activation of transversely oriented wave fronts in nonuniformly anisotropic myocardium is evident in the extracellular electrograms, which are highly fractionated (multiple deflections). Propagation parallel to the fibers is still fast, and electrograms are smooth with single deflections. Our anatomic, as well as electrophysiologic, data are compatible with such nonuniform anisotropic characteristics. An additional complicating factor for spread of activation arises, nonetheless, because of the changing direction of fibers in the anterior aspect of the triangle of Koch.

Relation with slow and fast pathway conduction. The classic model of AV conduction suggests two pathways with different conduction velocities and refractory periods in the environs of the triangle of Koch (18). Conduction velocity in the slow pathway is low and the refractory period is short; in contrast, the speed of conduction is high in the fast pathway, but its refractory period is long. These pathways have traditionally been considered anatomically discrete structures despite the lack of histologic evidence. It has, therefore, been proposed (6) that they are functional structures with directionally different effects on impulses because of the nonuniform anisotropic properties of the AV junction. Our data indeed show that conduction depends markedly on the site of stimulation. Although we found differences in speed of conduction during baseline stimulation from different sites, these differences were not reflected in the duration of the AH interval. Furthermore, during premature stimulation the increase of

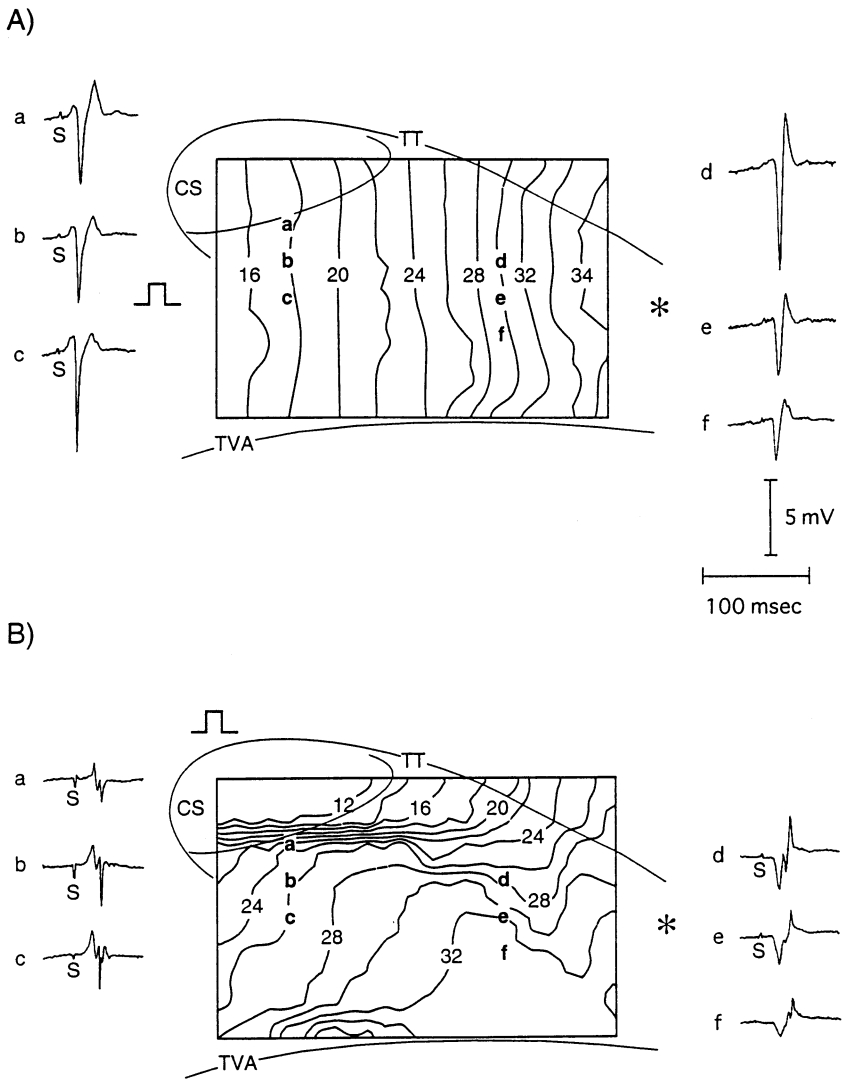

Figure 5. A, Extracellular electrograms recorded during propagation parallel to fiber direction (same activation map as in Fig. 3F). The preparation was stimulated from the left margin of the recording area (**marker**). Note that the electrograms reveal single deflections only. **B,** Electrograms recorded during propagation transverse to the fiber direction (same activation map as in Fig. 3E). The stimulation electrode was positioned at the upper left margin of the recording area. Electrograms are highly fractionated. **Arrows** indicate stimulus artifacts; S = stimulus; other abbreviations and markers as for Figure 3. See text for discussion.

conduction delay in the AV junctional area was only 10% of the increase of the AH interval. Thus, the increase in the AH interval can be only partly due to the increase in the conduction delay in the superficial layers of the AV junction. For these reasons it is unlikely that anisotropic conduction in the subendocardial layers of the AV junction plays an important role in slow AV conduction.

Limitations of the study. Our data show that anisotropy in dog and pig hearts contributes only marginally to the increase in the AH interval after premature stimulation. Recordings were made, however, only from the endocardial surface of the triangle of Koch. The AV junctional area is a complex three-dimensional structure, with activation not confined to superficial layers alone. Conduction delay must have occurred in deeper layers and escaped our attention. Thus, we cannot rule out that anisotropic conduction in deeper layers plays a role in the increase in the AH interval after premature stimulation.

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