Intercaval Block in Normal Canine Hearts
Role of the Terminal Crest
Ruediger Becker, MD; Alexander Bauer, MD; Stephan Metz, MD; Ralf Kinscherf, PhD; Julia C. Senges, MD; Kirsten D. Schreiner, MD; Frederik Voss, MD; Wolfgang Kuebler, MD, FACC; Wolfgang Schoels, MD

Background—The intriguing monotony in the occurrence of intercaval conduction block during typical atrial flutter suggests an anatomic or electrophysiological predisposition for conduction abnormalities.

Methods and Results—To determine the location of and potential electrophysiological basis for conduction block in the terminal crest region, a high-density patch electrode (10 × 10 bipoles) was placed on the terminal crest and on the adjacent pectinate muscle region in 10 healthy foxhounds. With a multiplexer mapping system, local activation patterns were reconstructed during constant pacing (S₁S₁ = 200 ms) and introduction of up to 2 extrastimuli (S₂, S₃). Furthermore, effective refractory periods were determined across the patch. If evident through online analysis, the epicardial location of conduction block was marked for postmortem verification of its endocardial projection. Marked directional differences in activation were found in the terminal crest region, with fast conduction parallel to and slow conduction perpendicular to the intercaval axis (1.1 ± 0.4 versus 0.5 ± 0.2 m/s, P < 0.01). In the pectinate muscle region, however, conduction velocities were similar in both directions (0.5 ± 0.3 versus 0.6 ± 0.2 m/s, P = NS). Refractory patterns were relatively homogeneous in both regions, with local refractory gradients not > 30 ms. During S₃ stimulation, conduction block parallel to the terminal crest was inducible in 40% of the dogs compared with 0% in the pectinate muscle region.

Conclusions—Even in normal hearts, inducible intercaval block is a relatively common finding. Anisotropic conduction properties would not explain conduction block parallel to the intercaval axis in the terminal crest region, and obviously, refractory gradients do not seem to play a role either. Thus, the change in fiber direction associated with the terminal crest/pectinate muscle junction might form the anatomic/electrophysiological basis for intercaval conduction block.

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Key Words: atrial flutter ▪ atrium ▪ conduction ▪ electrophysiology ▪ mapping

The intriguing monotony in the occurrence of intercaval conduction block during typical atrial flutter seems to indicate either an anatomic or an electrophysiological predisposition for conduction abnormalities. Experimental and clinical studies suggest that the terminal crest (TC) forms the anatomic substrate underlying intercaval conduction block. The well-known anisotropic conduction properties of the TC would readily explain conduction block perpendicular to but not parallel to the intercaval axis because of a reduced safety factor for propagation longitudinal to the fiber direction. Studies in isolated atrial preparations seem to indicate that conduction delay and block from the TC to the pectinate muscle region result from anatomic determinants such as collagenous septa and/or inhomogeneities in the distribution of gap junctions. Alternatively, electrophysiological determinants such as refractory gradients might play a role, although not apparent in in vitro preparations. On the basis of the hypothesis that the TC forms the anatomic substrate for functional conduction block across the intercaval region, conduction and refractory properties in the intercaval component of the TC and its ramifications into the right atrial appendage were studied in normal dogs to determine the anatomic location of and the potential electrophysiological basis for intercaval conduction block.

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From the University of Heidelberg, Department of Cardiology, and the Department of Anatomy III (S.M., R.K.), Heidelberg, Germany.
Correspondence to Ruediger Becker, MD, University of Heidelberg/Department of Cardiology, Bergheimer Str 58, 69115 Heidelberg, Germany. E-mail ruediger.becker@med.uni-heidelberg.de
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response. Third, activation patterns were reconstructed online during the AT of adjacent electrode sites differed by $\pm 40$ ms and if local isochrones comprising $\geq 3$ consecutive electrode sites, with adjacent electrode sites separated by $\geq 1$ isochronal line.

**Study Protocol**

In the TC and in the pectinate muscle region, the following protocol was applied. First, activation patterns were determined, and conduction times (CTs) for the TC and pectinate muscle region were calculated during constant pacing from the superior (parallel to intercaval axis) and posterior (perpendicular to intercaval axis) margins of the patch, respectively, at a cycle length of 200 ms (Figure 1). Second, local ERPs were measured along a line of 10 adjacent electrodes across the center of the patch perpendicular to the intercaval axis. After 8 basic stimuli at twice the diastolic threshold ($S_1$), an extrastimulus ($S_2$) was introduced, decreasing the $S_1S_2$ coupling interval in steps of 10 ms. The ERP was defined as the maximum $S_2$ potential that failed to evoke a propagated atrial response. Third, activation patterns were reconstructed online during the AT of adjacent electrode sites differed by $\pm 40$ ms and if local isochrones comprising $\geq 3$ consecutive electrode sites, with adjacent electrode sites separated by $\geq 1$ isochronal line.

**Mapping Technique**

For high-resolution mapping of the in situ canine lateral right atrial wall, a custom-designed, square patch containing $10 \times 10$ bipoles (interelectrode distance, 1.5 mm) was sutured epicardially on the intercaval component of the TC (Figure 1, position 1) and on the adjacent pectinate muscle region (Figure 1, position 2). A Biotronik UHS 20 stimulator (Biotronik GmbH&Co KG) was used for pacing and determination of effective refractory periods (ERPs). Mapping data were simultaneously processed through a 256-channel multiplexer and recorded on videotape for offline digitization and computer analysis (bandwidth, 20 to 500 Hz; sampling rate, 1000 Hz). The mapping system used was developed at the University of Limburg (Maastricht, the Netherlands). At each recording site, local activation time (AT) was determined automatically on the basis of the maximal first derivative as in comparable previous studies.1,20 Each marking was reviewed and manually revised if necessary. In multiphasic signals lacking a sharp intrinsic deflection, the peak of the major deflection was chosen as the moment of activation. ATs were calculated relative to the pacing artifact. From these ATs, 2D isochronal activation maps were constructed manually at 10-ms intervals. As detailed previously, conduction block was assumed if the AT of adjacent electrode sites differed by $\pm 40$ ms and if local isochrones comprising $\geq 3$ consecutive electrode sites, with adjacent electrode sites separated by $\geq 1$ isochronal line.

**Results**

**Conduction Properties During $S_1$ Stimulation**

In the TC region, marked directional differences in CT/conduction velocity were found, with significantly faster conduction parallel to compared with perpendicular to the intercaval axis. In the adjacent pectinate muscle region, however, no statistically significant directional differences in CT were encountered, although there was a tendency toward faster conduction perpendicular to the intercaval axis. The data are summarized in Table 1. In Figure 2, typical activation patterns from both regions have been selected, displaying very fast conduction along the TC (Figure 2A) compared with relatively slower propagation perpendicular to the intercaval axis in the TC region (Figure 2B) and in the pectinate muscle region, where similar activation patterns and CTs were evident almost independently of the direction of impulse propagation.

**Effects of $S_2$ and $S_1$ Stimulation on Conduction Perpendicular to the Intercaval Axis**

Compared with $S_1$ stimulation, conduction perpendicular to the intercaval axis was significantly delayed during $S_2$ stim-
ulation in both the TC and the pectinate muscle region (Table 2). However, no evidence of conduction block was found in any dog. During S3 stimulation, conduction perpendicular to the intercaval axis was further delayed compared with S2 stimulation (Table 2), but no complete conduction block occurred in the pectinate muscle region. In the TC region, however, S3 stimulation induced lines of conduction block parallel to the intercaval axis in 4 of 10 dogs ($P < 0.05$ versus pectinate muscle region). As a result, S3 stimulation more markedly prolonged CTs in the TC than in the pectinate muscle region (Table 2). In dogs exhibiting conduction block at S3 stimulation, CT perpendicular to the intercaval axis at S1 stimulation was significantly longer than in dogs without conduction block (36±7 versus 24±2 ms, $P < 0.05$). In Figure 3, typical examples of activation patterns are displayed that were obtained during extrastimulation in the TC (Figure 3A) and in the pectinate muscle region (Figure 3B) and are complemented by original electrogram tracings. In the pectinate muscle region (Figure 3B), conduction spread centrifugally and homogeneously from the pacing site at the anterior edge toward the posterior edge of the patch and toward both sides, with the CT across the patch delayed to a greater extent during S3 compared with S1 stimulation (65 versus 54 ms). Activation patterns were otherwise very similar. In the TC region (Figure 3A), conduction was more markedly delayed during S2 stimulation, particularly in the central part of the multielectrode; however, no complete conduction block occurred. With the introduction of a second extrastimulus (S3), a line of conduction block was encountered separating the third from the fourth row of electrodes on the superior and the fourth from the fifth row of electrodes on the inferior margin of the patch, respectively. The direction of activation in the area distal to the block was changed markedly, displaying a pattern consistent with 2 colliding wavefronts entering through both sides of the patch. Postmortem examination revealed that the epicardial line of block exactly matched the endocardial location of the TC (Figure 4). This was true for all dogs exhibiting complete conduction block.

In a subgroup of dogs ($n = 5$), extrastimulation was performed from both the anterior and posterior margins of the multielectrode (distance between anterior and posterior pacing sites and TC, 4.5 to 9 mm and 3 to 6 mm, respectively). In 2 of those dogs, complete conduction block across the TC was inducible. In both of them, the location of the block was independent of the site of pacing, as illustrated in Figure 5.

**Refractory Patterns Across the Intercaval Axis**

Refractory patterns were relatively homogeneous both in the TC and in the pectinate muscle region. Local ERP gradients

| Table 2. Conduction Times Perpendicular to the Intercaval Axis During S1, S2, and S3 Stimulation |
|--------------------------------------------------|--------------------------------------------------|
| CT S1, ms | CT S2, ms | CT S3, ms |
| TC region | 33±12 | 60±17* | 78±18† |
| Pectinate muscle region | 28±8 | 54±12* | 60±15† |

* $P<0.001$ vs CT S1; † $P<0.01$ vs S3; ‡ $P<0.05$ vs S1 (Student’s t test for paired data).
did not exceed 30 ms in both areas, with no obvious differences in the frequency or distribution of peak gradients. Mean refractory gradients did not differ either (Table 1). However, mean ERP was slightly longer in the pectinate muscle compared with the TC region (Table 1). Even in areas with proven conduction block during S3 stimulation, there was no systematic decrease or increase in local refractoriness, and no significant refractory gradients could be observed.

Histology
To elucidate the role of regional ultrastructure for the occurrence of conduction block, arrangement and continuity of muscle bundles, as well as distribution and amount of connective tissue, were analyzed in multiple sections of the TC and its transition to the pectinate muscles and to the SV. Sections were obtained in steps of \( \approx 100 \mu m \) from epicardial to endocardial layers. A representative example is depicted in Figure 6. Histological findings in a dog with (dog 6) and a dog without (dog 10) conduction block are shown for comparison. In both animals, the TC consisted of a broad band of parallel muscle bundles. Within these bundles, the muscle cells were closely packed, and branches of smaller bundles were ramified toward the pectinate muscle region and toward the SV. In both dogs, the muscle bundles continued from the TC to the pectinate muscles over a thickness of \( \approx 1000 \mu m \). No obvious differences were observed between both dogs in terms of arrangement and continuity of muscle cells at the ramification area between the TC and pectinate muscles. Both gradual changes in fiber direction with longitudinally contacting muscle cells and abrupt changes with orthogonally contacting muscle cells were found in each dog (Figure 6A and C). The transition between the TC and the SV was not as regular as the transition between pectinate muscles and the TC; however, continuous connections between the muscle fibers were always present (Figure 6B and D); the muscle bundles were less tightly arranged, and the amount of connective tissue was increased considerably. Generally, no clear boundary between the TC and SV was seen in both animals (Figure 6B and D). Within the connective tissue, the muscle cells were connected in a netlike manner. In summary, obvious histological differences potentially explaining the occurrence of conduction block could not be demonstrated. This was true not only for the arrangement of muscle bundles in the TC and its transition toward both the pectinate muscles and the SV but also for the arrangement and amount of connective tissue.

Discussion
To the best of our knowledge, this is the first high-resolution mapping study to specifically compare directional conduction and refractory properties in the intercaval component of the TC and its ramifications into the right atrial appendage. Not only were we able to confirm the markedly anisotropic conduction properties of the TC region previously suggested
by multipolar electrode catheter recordings, but we also demonstrated that conduction velocities perpendicular and transverse to the intercaval axis do not differ significantly in the adjacent pectinate muscle region, probably because of a more complex, nonuniform anisotropic texture. Furthermore, apart from significantly delaying conduction perpendicular to the intercaval axis in both the TC and the pectinate muscle region, the use of 2 extrastimuli (S1, S2) induced functional conduction blocks exactly overlying the TC in 40% of dogs. In contrast, no evidence of complete conduction block was ever encountered in the pectinate muscle region. With respect to the mechanism of conduction block, refractory gradients are unlikely to play a role, because ERPs and peak refractory gradients did not differ significantly between both regions. Our data confirm the hypothesis that the TC provides an anatomic basis for functional conduction block across the intercaval region.2,5 Our findings in whole animals argue against a contribution of refractory gradients to the genesis of conduction block, at least under physiological conditions. Refractory gradients were generally insignificant, and above all, the TC region did not differ from the pectinate muscle region with respect to peak and mean local refractory gradients despite obvious differences in the propensity for conduction block.

**Comparison With Other Studies**

Using multipolar mapping catheters to study conduction perpendicular to the intercaval axis in patients with atrial flutter, previous studies have demonstrated marked conduc-

tion delay and split potentials, suggesting that the TC forms an anatomic substrate for functional conduction block across the intercaval region.6–14 Combining high-resolution mapping with postmortem analyses in normal dogs, we could confirm that rate-dependent conduction block epicardially coincides with the endocardial projection of the TC and that this phenomenon was rather common even in normal hearts (40%). Pacing from both the anterior and posterior margins of the multielectrode in a subgroup of dogs (n = 5) ruled out an additional line of block in the adjacent SV region.21 In contrast to the TC region, no evidence of conduction block was found in the adjacent pectinate muscle region in any dog. The well-known anisotropic conduction properties of the TC would readily explain conduction block perpendicular to but not parallel to the intercaval axis because of a reduced safety factor for propagation longitudinal to the fiber direction.15 However, experimental studies analyzing conduction properties in isolated TC preparations have elucidated that changes in the direction of cellular connections relative to the direction of propagation predispose to unidirectional conduction block.2,4 Specifically, branch sites of pectinate muscles from the TC, particularly with acute angles,7 were suggested to predispose to conduction block, probably because of an increase in effective axial resistivity.4 Histology performed in the present study did not demonstrate systematic differences in myocardial texture at the transition between the TC and pectinate muscles; of note, branch angles exhibited a marked intranidividual variation through the different myocardial layers, rendering a direct relation between the acuity of branch angles and the occurrence of conduction block very unlikely. However, independent of specific branch angles, the change in fiber direction may represent an area of nonuniform anisotropy prone to conduction block. Although this study failed to demonstrate obvious differences in amount or distribution of connective tissue, collagenous septa might also play a role.16 As suggested by previous experimental findings, the predisposition of the TC for conduction block might be related to a characteristic distribution of gap junctions; specifically, a preponderance of end-to-end and a relative paucity of side-to-side connections have been described that apparently are associated with a characteristic distribution of the channel proteins connexin 40, 43, and 45.17,18 These findings provide an alternative explanation for transverse conduction block across the TC.

Theoretically, the occurrence of conduction block across the TC could also be related to specific refractory patterns. Studies in isolated atrial preparations have been inconsistent with respect to the presence of refractory gradients across the TC.2,5 Our findings in whole animals argue against a contribution of refractory gradients to the genesis of conduction block, at least under physiological conditions. Refractory gradients were generally insignificant, and above all, the TC region did not differ from the pectinate muscle region with respect to peak and mean local refractory gradients despite obvious differences in the propensity for conduction block.

**Methodological Considerations**

The mapping area was limited to the intercaval component of the TC and its ramifications into the right atrial appendage,
and conduction in the smooth-walled intercaval myocardium was not analyzed. The findings presented must be considered specific to this particular region and do not necessarily apply to other sections of the TC.

As far as the differentiation between marked slow conduction and conduction block is concerned, various criteria have been extensively studied and discussed in earlier high-resolution mapping studies. Accordingly, the criteria used in the present study have been established and widely used in comparable mapping studies. However, it still remains difficult to differentiate with certainty between marked slow conduction and conduction block. In anisotropic atrial preparations, minimal CTs in the range of 0.04 to 0.12 m/s have been measured during impulse propagation transverse to the fiber direction compared with 1.0 to 1.3 m/s longitudinal to the fiber direction. Theoretically, marked slow conduction therefore might have been misinterpreted as complete conduction block. However, independent of definitions, conduction delay as marked as this forms a potential basis for reentrant arrhythmias and as such is expected to exert similar functional effects.

Because of the limited size of the multielectrode used, the length of induced conduction blocks could not be determined, because all blocks approached or exceeded the dimensions of the patch (≥15 mm). Furthermore, the indiscernibility of atrial tachyarrhythmias was not systematically studied. This could have helped us to appreciate potential functional effects of conduction abnormalities.

Clinical Implications

The inducibility of functional conduction block across the TC even in normal canine atria supports the hypothesis of an anatomically determined predisposition to conduction abnormalities, thus providing the substrate for a central obstacle in a macroreentrant circuit. The presence of an anatomically determined substrate for reentry might explain the occasional occurrence of (typical) atrial flutter in human atria.

The presence of an anatomically determined substrate for conduction block, the cavotricuspid "isthmus" region remains the primary target site for therapeutic interventions such as radiofrequency ablation.

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