Tissue-Specific Determinants of Anisotropic Conduction Velocity in Canine Atrial and Ventricular Myocardium

Jeffrey E. Saffitz, H. Lee Kanter, Karen G. Green, Timothy K. Tolley, Eric C. Beyer

Abstract  Electrical conduction is very rapid and highly anisotropic in atrial fiber bundles, such as the crista terminalis. In contrast to left ventricular myocardium in which the ratio of longitudinal to transverse conduction velocities is =3, propagation velocity in the crista terminalis is =10 times greater in the longitudinal than in the transverse direction. To elucidate potential determinants of these distinct conduction properties, we characterized structural and molecular features of intercellular coupling in the crista terminalis and left ventricular myocardium of the canine heart. Analysis of the number and spatial orientation of myocyte interconnections at gap junctions revealed that a typical left ventricular myocyte was connected to 11.3±2.2 other myocytes. Approximately equal numbers of connections occurred between ventricular myocytes juxtaposed in side-to-side and end-to-end orientation. In contrast, a typical myocyte of the crista terminalis was connected to only 6.4±1.7 other cells (P<.05), but nearly 80% of these connections occurred between cells oriented in an end-to-end configuration. In comparison with the ventricular pattern, this spatial distribution of connections would limit intercellular current transfer between laterally apposed cells and thereby enhance anisotropy of conduction velocity in the longitudinal and transverse directions. Ultrastructural analysis showed that crista terminalis myocytes were connected by numerous small gap junctions that occurred in relatively simple, straight intercalated disks. Northern blot analysis showed approximately equivalent amounts of mRNAs encoding the gap junction channel proteins connexin43 and connexin45 but approximately four times more connexin40 mRNA in crista terminalis than in the left ventricle. Immunocytochemical studies with connexin-specific antibodies revealed far more intense connexin40 signal in crista terminalis than in left ventricular muscle. Thus, myocytes of the crista terminalis and left ventricular subepicardium differ markedly in the number and spatial distribution of their intercellular junctions and in the molecular composition of their gap junction proteins. These structural and molecular features likely contribute to the distinct anisotropic conduction properties characteristic of the two tissues. (Circ Res. 1994;74:1065-1070.)

Key Words  • crista terminalis • anisotropic conduction • gap junctions • connexins • immunofluorescence • morphometry

Conduction velocities vary widely in specific tissues of the mammalian heart, such as atrial and ventricular myocardium, and the nodes and bundles of the cardiac conduction system.1-4 Active membrane properties certainly play a major role in determining conduction properties (eg, the physiological absence of fast sodium currents in slowly conducting atrioventricular node tissue), but the passive properties including the extent and spatial distribution of cytoplasmic and junctional resistances to current flow are also important determinants.4-5 These passive properties are specified mainly by structural features, such as the size and elongated shape of individual myocytes, as well as the size, number, and three-dimensional distribution of gap junctions that interconnect cells in tissue. Because specific tissues of the mammalian heart express different amounts of the three physiologically distinct cardiac gap junction channel proteins (connexins),6-10 differences in the molecular composition of gap junction channels may also help to determine characteristic conduction properties of cardiac tissues.

Examples of tissues in which disparate passive properties may contribute to differences in conduction properties are the crista terminalis of the right atrium and the left ventricle. Longitudinal propagation in defined atrial fiber bundles such as the crista terminalis is not only extremely rapid but also highly anisotropic. Conduction velocity in the crista terminalis is =10 times more rapid in the longitudinal direction (parallel to fiber orientation) than in the transverse direction (perpendicular to the long cell axis).4-5 In contrast, a directional difference of only =3:1 has been observed in ventricular muscle.1-4 Although atrial and ventricular muscle differ in their active sarcolemmal membrane ionic currents, these properties cannot account for their disparate tissue anisotropy. To elucidate potential mechanisms that might explain these conduction properties, we performed the present study to compare structural and molecular features of intercellular coupling in canine crista terminalis and left ventricular myocardium.

Materials and Methods

Tissue Acquisition

Samples of crista terminalis and subepicardium of the anterior left ventricular free wall were dissected from hearts excised from five adult mongrel dogs anesthetized with 20 mg/kg IV sodium thiopental. Some tissue samples were frozen immediately and stored at −70°C for subsequent immunocytochemical analysis and extraction of total RNA for Northern
blot analysis. The remaining tissue samples were fixed for high-resolution light and electron microscopy by immersing small fragments in a fixative composed of 2% glutaraldehyde, 1% paraformaldehyde, and 2 mmol/L calcium chloride in 0.08 mol/L sodium cacodylate buffer (pH 7.4).

**Light Microscopic Reconstructions of the Spatial Distribution of Intercellular Connections**

Tissue blocks measuring \(1 \times 1 \times 0.5\) mm, dissected and fixed as described above, were postfixed for 15 minutes in 1% osmium tetroxide containing 1% potassium ferrocyanide, dehydrated in ethanol, and embedded in Spurr's resin. The addition of potassium ferrocyanide enhanced subsequent sarcolumellar staining, thereby facilitating identification of cell borders and junctional membranes at the light microscopic level of resolution.

A series of 40 consecutive sections, each \(1.5\) \(\mu\)m in thickness, was cut in a plane longitudinal to the long fiber axis from at least two tissue blocks from each crista terminalis (10 sets of serial sections) and two blocks from two of the left ventricular subendocardial samples (four sets of serial sections). The sections were mounted sequentially on slides and stained with toluidine blue. Two individual index cardiac myocyte profiles were randomly selected in the 20th section of each set of 40 serial sections, and these index cells and all neighboring myocytes to which they were connected by intercalated disks were delineated and counted by identifying, in their entirety, profiles of these cells in sections 19 and below sections and above. A cellular interconnection was tabulated only after an intercalated disk between the adjacent cells was identified unequivocally. It was assumed that the presence of one or more intercalated disks connecting two cells identified at the light microscopic level of resolution indicated electrical interconnection at gap junctions. This assumption is based on observations by others that at least one and usually several gap junctions occur at each intercalated disk.

In addition to measuring the number of cells connected to each index cell in each set of serial sections, we characterized the spatial distribution of each interconnection on the basis of its relative side-to-side or end-to-end orientation according to a system devised in our previous studies. Four classes of interconnections were defined as follows: type I, >75% of the lateral borders of the two cells overlap; type II, 25% to 75% lateral border overlap; type III, <25% lateral border overlap and <50% end-to-end overlap; and type IV, <25% lateral border overlap and >50% end-to-end overlap. A schematic diagram of these categories is included in Fig 1. The maximum length and width of each index cell was also measured in selected sections. In all, 20 index cells were analyzed in crista terminalis samples (4 cells in samples from each of five animals), and 8 cells were analyzed in left ventricular subepicardial samples (4 cells in each of two hearts).

**Ultrastuctural Morphometry of Intercellular Connections in Crista Terminalis**

Ultrathin sections for electron microscopic analysis were prepared from each block of crista terminalis from which serial sections had been cut for light microscopic analysis of intercellular connections. Ultrathin sections were collected on 200-mesh copper-rubidium grids and stained with uranyl acetate and lead citrate as described previously and examined with a JEOL 1200EX transmission electron microscope.

Ultrathin sections were cut first in a longitudinal plane parallel to the long fiber axis, and then, after reorienting the block in the microtome, additional sections were prepared in a plane transverse to the long fiber axis to produce cross sections in a myocyte. At least 4 separate randomly selected test areas from each crista terminalis sample were analyzed morphometrically. In all, 28 test areas were analyzed in crista terminalis samples sectioned in the long orientation, and 30 test areas were analyzed in samples sectioned in an axis transverse to the long cell axis.

Ultrastuctural morphometric analysis was performed by use of methods described previously. Individual test regions were first photographed at a final print magnification of \(5000\). The total area occupied by cardiac myocytes was measured in each individual test area in these low-magnification micrographs. In addition, all portions of each test area containing intercalated disks and gap junction profiles were photographed again at high magnification for further analysis (final print magnification, \(25000\)). The lengths of intercalated disk and gap junction profiles were measured in these high-power micrographs by use of an electronic pen and digitizing tablet (Houston Systems, Inc). Data were expressed as gap junction profile length or profile number per 100-\(\mu\)m intercalated disk length. In all, 65 high-power micrographs containing 97 junctional profiles in the long orientation and 55 micrographs containing 110 profiles in the transverse orientation were analyzed.

**Northern Blot Analysis**

Total cellular RNA was extracted from samples of crista terminalis and left ventricular epicardium from each of three dogs by use of the guanidinium thiocyanate–phenol–chloroform procedure as described previously. RNA (10 \(\mu\)g of each sample) was electrophoresed on formaldehyde/agarose gels, transferred to nylon membranes, and cross-linked with ultraviolet light as described previously. Specific [\(^{32}P\)]dCTP-labeled DNA probes, shown in previous studies, to hybridize specifically with mRNA for the three mammalian cardiac connexins (connexin43 [Cx43], connexin40 [Cx40], and connexin45 [Cx45], were synthesized by the random primer technique. The blots were hybridized for 18 hours at 65°C, washed stringently, and analyzed by autoradiography as previously described. In some experiments, a probe corresponding to mouse 18S ribosomal RNA was used as a control to ensure that equivalent amounts of total RNA were loaded from each sample.

**Immunofluorescence Analysis**

Sections (12 \(\mu\)m in thickness) of rapidly frozen unfixed crista terminalis and left ventricular subepicardium were prepared in a cryostat and mounted on gelatin-coated slides. Sections were washed in phosphate buffered saline (PBS) and preincubated for 30 minutes in a blocking buffer composed of 3% normal goat serum, 0.4% milk protein, 2% IgG-free bovine serum albumin, and 0.3% Triton X-100 in PBS. Sections were incubated with monospecific antibodies against Cx43, Cx40, and Cx45. The primary antibodies used in immunocytochemical studies have been extensively characterized in previous studies. Cx43 was detected with a mouse monoclonal IgG antibody raised against amino acids 252 to 270 of rat Cx43 (Chemicon International, Inc). Cx40 was detected with an affinity-purified polyclonal rabbit antibody raised against residues 316 to 329 of dog Cx40. Cx45 was detected with an affinity-purified rabbit polyclonal antibody raised against residues 2485 to 298 of dog Cx45. Previous immunoprecipitation and immunofluorescence experiments have demonstrated that none of these antibodies cross-reacts with another cardiac connexin. Sections were incubated overnight with 1:400 dilutions of primary antibody mixed in blocking buffer. Normal nonimmune mouse and rabbit sera were used as negative controls. After being incubated with primary antibodies, sections were rinsed in PBS and incubated with appropriate rabbit or mouse secondary antibodies conjugated to CY3 (Jackson Immuno Research Laboratories) and diluted 800-fold.

**Statistical Analysis**

Morphometric data were expressed as mean ± SD. Differences between the number and orientation of crista and ventricular myocyte interconnections and between morpho-
metric values measured in longitudinal and transverse orientations in crista myocytes were determined with unpaired $t$ tests. A value of $P<.05$ was considered to indicate a significant difference.

**Results**

The number and spatial orientation of myocyte interconnections determined by three-dimensional reconstructions in serial sections of crista terminalis and left ventricle are shown in Fig 1. In the left ventricle, randomly selected ventricular myocytes were found to have $11.3\pm2.2$ neighbors to which each was connected at intercalated disks. Approximately 29% of interconnected cells were juxtaposed in a purely side-to-side orientation (type I connections) and 34% were oriented end to end (type IV junctions). If type I and type II junctions are considered to represent interconnections between cells in a pure or predominant side-to-side orientation and type III and type IV junctions occur between neighbors in a pure or predominant end-to-end orientation, then approximately half of the total cellular interconnections in ventricular muscle occurred between cells oriented side to side, and the remaining half occurred between cells oriented end to end. These observations regarding the number and spatial orientation of interconnections in canine left ventricle are virtually identical to results reported in our previous studies.\(^{11,12}\)

In contrast to the architecture of the left ventricle, a markedly different pattern of intercellular connections was observed in the crista terminalis. Randomly selected myocytes of the crista were connected by intercalated disks to $6.4\pm1.7$ individual cells ($P<.05$ versus left ventricular myocytes). The great majority of interconnections occurred between cells oriented in end-to-end apposition. Of the 6.4 neighbors to which the average crista terminalis myocyte was connected, 3.8 (60%) of the neighbors had type IV connections and an additional 1.1 (19%) had type III connections. Thus, more than three fourths of the interconnections in the crista terminalis occur between myocytes juxtaposed in a purely or predominantly end-to-end orientation. Even though ventricular myocytes are connected to twice as many neighbors as crista terminalis myocytes, the number of interconnections between cells in end-to-end orientation (type IV connections) are equivalent in the two tissues (3.9±1.1 type IV connections per myocyte in ventricle and 3.8±1.1 type IV connections to each myocyte of the crista terminalis, $P=NS$).

**Table 1.** Maximal Length and Width of Index Myocytes Analyzed in Serial Sections

|                | Length, \(\mu m\) | Width, \(\mu m\) | Length: \
|----------------|-------------------|-----------------|-----------
| Left ventricle (n=8) | 122.1±13.9 | 23.3±3.5 | 5.2 |
| Crista terminalis (n=20) | 96.4±18.2 | 18.7±5.0 | 5.2 |

Values are mean±SD. *$P<.05$ vs corresponding values for left ventricle.

The mean maximal length and width measurements of the index ventricular and crista terminalis myocytes are shown in Table 1. Ventricular myocytes were $\approx25\%$ longer and 25% wider than crista terminalis myocytes ($P<.05$ for both), but the length-to-width ratios were identical. The values for ventricular myocytes are similar to previously reported data.\(^{11,12}\) These measurements may have been underestimated, however, because the maximal dimensions of topographically complex myocytes are not always evident in single slices through the tissue. Nevertheless, the morphometric data indicate that the disparate anisotropic conduction properties of the two tissues are not attributable to differences in the cell length-to-width ratio.

Ultrastructural analysis confirmed and extended the light microscopic findings. A representative electron micrograph (Fig 2) shows the relatively simple, straight intercalated disks that typically connect crista terminalis myocytes in an end-to-end fashion. Morphometric analysis revealed that myocytes of the crista terminalis are interconnected by numerous small junctions, having a mean profile length of $=0.3\ \mu m$ in both long and transverse planes of section (Table 2). Approximately 12 individual gap junction profiles were observed for each 100 \(\mu m\) of intercalated disk length analyzed. No significant differences were observed in morphometric parameters measured in sections cut in the transverse and longitudinal planes of section. Thus, in contrast to ventricular muscle in which previous studies have identified a subclass of very long anisotropic junctions with their long axes oriented transverse to the long cell axis,\(^{11,12}\) gap junctions between atrial myocytes of the crista terminalis are small and isotropic in structure.

Fig 3 is a representative Northern blot showing the relative abundance of mRNA transcripts for the three mammalian gap junction proteins, Cx43, Cx40, and Cx45. Both crista terminalis and left ventricular myocardium contained abundant Cx43 mRNA transcripts. Under comparable gel loading and film exposure conditions, the Cx45 signal was weak, although it appeared that the crista contained slightly more Cx45 mRNA than did the ventricle. The same relative proportions of Cx43 and Cx45 mRNA have been observed in previous studies of canine ventricular muscle.\(^{6,7}\) In contrast, approximately four times more Cx40 mRNA was observed in the atrial samples than in the ventricle. A similar pattern of three Cx40 bands has been observed in Cx40 transcripts isolated from canine Purkinje fibers\(^7\) and aorta\(^8\) and may represent differential mRNA splicing. Densitometric analysis of 18S RNA bands confirmed that approximately equal amounts of total cell RNA were loaded in each lane. Thus, although the crista terminalis and ventricular muscle express roughly equivalent amounts of Cx43 and Cx45, they differ substantially in the amount of Cx40 mRNA they express.

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**Fig 1.** Chart showing the number and spatial orientation of cells interconnected to randomly selected myocytes in normal canine ventricular epicardium and crista terminalis. Numbers in parentheses indicate the percentage of each connection type in the two tissues. Data are expressed as mean±SD, and asterisks indicate significant differences between the number of connections of each type in the ventricle and crista terminalis. Type I connections are purely side to side, type IV connections are purely end to end, and types II and III exhibit variable side-to-side and end-to-end orientations. *$P<.001$, **$P<.02$.
To determine whether the observed differences in Cx40 mRNA expression were also reflected at the protein level, we performed immunocytochemistry on frozen sections of crista terminalis and left ventricle by use of methods extensively validated in previous studies. As shown in Fig 4, Cx43 and Cx45 immunoreactivity was readily identified in both tissues. In contrast, Cx40 staining was far more intense in the crista terminalis than in the left ventricular muscle, consistent with Northern blot analysis in the present study and with previous studies showing modest Cx40 expression in canine ventricular muscle. In addition, the patterns of connexin immunofluorescence (with all antibodies) were strikingly different in crista terminalis and the ventricle. As shown in Fig 4, junctions between atrial myocytes occurred in relatively simple, straight intercalated disks that connected cells in a predominant end-to-end fashion. In contrast, the pattern of immunostaining in ventricular muscle reflected the far more extensive gap junctions between ventricular cells juxtaposed in side-to-side as well as end-to-end orientation.

**Discussion**

The results of the present study indicate that myocytes of the canine crista terminalis and the left ventricular subepicardium differ markedly in the number and spatial distribution of their intercellular junctions and the molecular composition of their gap junctional proteins. The structural differences in the two tissues were most striking. Although myocytes of both the crista terminalis and left ventricle have a roughly cylindrical shape with equivalent length-to-width ratios, ventricular myocytes have numerous small intercalated disks and gap junctions that occur at the ends of groups of peripheral sarcomeres that terminate at selected points along the cell body. The presence of these multiple "end processes" permits the complex packed packing of ventricular myocytes in tissue with interconnections between cells in varying degrees of end-to-end and side-to-side orientation. Thus, as observed in previous studies and confirmed in the present study, a typical ventricular myocyte is connected to an average of 11 or 12 other myocytes, and equivalent numbers of junctions occur between neighbors in side-to-side and end-to-end apposition. As a result, wave fronts moving

**TABLE 2. Ultrastructural Morphometric Values Measured in Ultrathin Sections of Crista Terminalis Sectioned in Planes Longitudinal and Transverse to the Long Cell Axis**

<table>
<thead>
<tr>
<th></th>
<th>Longitudinal Plane</th>
<th>Transverse Plane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gap junction profile length (µm) per 100 µm intercalated disk length</td>
<td>3.2±2.4</td>
<td>3.8±2.1</td>
</tr>
<tr>
<td>Number of gap junction profiles per 100 µm intercalated disk length</td>
<td>11.5±7.4</td>
<td>12.2±7.6</td>
</tr>
<tr>
<td>Mean gap junction profile length, µm</td>
<td>0.28±0.07</td>
<td>0.33±0.12</td>
</tr>
</tbody>
</table>

Values are mean±SD.

No significant differences were found between values measured in the two orientations, indicating a lack of structural anisotropy in the junctions.

**Fig 2.** A representative electron micrograph of the crista terminalis. Myocytes are connected in an end-to-end fashion by relatively simple intercalated disks (arrows) that do not have the complex staircase configuration characteristic of the ventricle. The lateral margins of individual cells are relatively smooth and do not exhibit "end processes" that form interconnections between laterally apposed cells.

**Fig 3.** A Northern blot (representative of three experiments) of connexin (Cx) mRNAs in canine left ventricular myocardium (LV) and crista terminalis. Ten micrograms of total RNA was loaded in each lane. Autoradiographs were developed after 18 hours of film exposure.
through ventricular muscle in the transverse direction (perpendicular to the long cell axis) encounter numerous intercellular junctions. The slower transverse conduction velocity appears to be due primarily to the cylindrical shape of the individual cells such that the transversely propagating wave front would encounter many more junctions than would a wave front traveling an equal distance in the longitudinal direction and thus would experience greater resistance.

In contrast to the complex topography of ventricular myocytes, myocytes of the crista terminalis are more smoothly cylindrical and have relatively few "end processes." The intercalated disks of crista terminalis myocytes are relatively straight and are typically located at the true ends of the cells. Thus, although these myocytes are connected to fewer neighbors than ventricular myocytes, most of the connections occur between cells oriented end to end. This packing geometry, delineated in three-dimensional reconstructions, was readily apparent at the ultrastructural level of resolution and in immunocytochemical preparations of atrial junctions that showed a connexin staining pattern that was distinctly different from that of the ventricle.

Additional differences in the structure of intercellular junctions of ventricular and atrial myocytes were discovered in ultrastructural morphometric studies. In previous work, we found that ventricular myocytes have two different structural classes of junctions: numerous small discoid junctions occur within plicate segments of the intercalated disk, and larger ribbon-shaped junctions with their long axes oriented perpendicular to the long cell axis are located in interplicate segments between offset plicate regions. The latter class of anisotropic junctions are less numerous but, because of their large size, account for a substantial proportion of total gap junctional density in the ventricle. In contrast, the myocytes of the crista terminalis contained numerous small discoid junctions but few of the large junctions. Thus, morphometric parameters of gap junction density and junction profile length were similar in ultrathin sections cut parallel and perpendicular to the long cell axis. Virtually all of the atrial junctions are aligned in rather straight intercalated disks at the true ends of the cells, thus accounting for the immunohistochemical appearance of the atrial connections in preparations stained with anticonnexin antibodies.

The highly anisotropic arrangement of intercellular connections in the crista undoubtedly contributes to the large directional differences in conduction velocity characteristic of this tissue. Transverse propagation in the crista terminalis would appear to be greatly impeded by the relative paucity of connections between cells in side-to-side apposition and the resultant increase in resistance to current propagation in the transverse direction.

In addition to the marked structural differences that characterize interconnections between myocytes of the crista terminalis and ventricle, we also observed a major difference in the connexin phenotype of these two tissues. Interestingly, Manjunath and Page have reported differences in the relative solubilities of rat atrial and ventricular gap junctions in selected detergents, perhaps reflecting the different connexin composition of junctions in these tissues. However, although there may be biochemical differences between atrial and ventricular junctions, the functional implications of these bio-

![Photomicrographs showing immunohistochemical delineation of connexin43 (top panels), connexin45 (middle panels), and connexin40 (bottom panels) expression in the left ventricle (right panels) and crista terminalis (left panels). Connexin40, connexin43, and connexin45 immunoreactivity are readily apparent in the crista terminalis in a pattern consistent with the relatively simple, straight intercalated disks observed in morphometric studies. In contrast, the staining pattern of ventricular junctions is more complex, consistent with the extensive side-to-side and end-to-end interconnections. Connexin40 immunoreactivity in the ventricle is considerably less intense than in the crista.](image-url)
chemical or molecular differences are not so readily apparent. We have observed greater expression of Cx40 in canine Purkinje fibers than in ventricular muscle and have speculated that because Cx40 has been found to form channels with greater unitary conductance than Cx43, enhanced Cx40 expression may be associated with lower junctional resistance and greater conduction velocity. However, we have recently found that both the sinus and atrioventricular nodes of the canine conduction system also express abundant amounts of Cx40 (although they also appear to lack Cx43). Thus, enhanced Cx40 expression occurs in disparate tissues characterized by very rapid and very slow conduction. It is possible that regulation of channel gating or conductance states may differ in specific tissues of the heart, but at the present time, the biological significance of specific connexin phenotypes is unknown. Bastide et al. have recently reported that Cx40 expression in the rat is enhanced in ventricular myocyte layers close to the endocardium. However, in the present studies, connexin expression was analyzed in subepicardial samples of canine left ventricle, which were found to have lower levels of Cx40 mRNA and protein expression than the crista terminalis.

In conclusion, our observations suggest that architectural features of individual cells and the three-dimensional distribution of intercellular junctions may vary widely in the heart and likely contribute to the distinct conduction properties of specific cardiac tissues. In view of recent evidence that connexin expression may be developmentally regulated in chick and rodent hearts, the results of the present study suggest further experiments on developmental and aging effects on anisotropic conduction velocity ratios. Perhaps regional or developmental differences in connexin expression could have functional consequences similar to those reported by Spach et al. regarding the expression of troponin T isoforms and the distribution of repolarization properties in adult and newborn dogs. Our results also underscore the potential importance of consideration of cell shape and cell packing geometry in realistic two-dimensional or three-dimensional tissue models designed to explore longitudinal or transverse propagation in individual cells.

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