Genesis of High Frequency Notching of QRS Complexes in an In Vivo Cardiac Model

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SUMMARY

High frequency notching of the QRS complex is associated with transmural infarction, cardiomyopathies, and ventricular hypertrophy from any cause. The mechanism producing notching is unknown; but the presence of a discrete anatomic lesion is not an essential feature. The hypothesis that notching was produced by activation across, rather than along, myocardial fibers was investigated by stimulation at 12 points around a clock electrode attached to the epicardium while mapping isochronous lines in the area activated. All fibers at the subendocardial layer beneath the clock electrode were ligated by a purse-string suture. Propagation direction, as measured by isochronous maps, produced more notched QRS complexes when the path was across, rather than parallel with, the myocardial fibers. Using grouped data and a 5 × 6 table, notches versus the angle formed between fiber direction and orientation of the direction of travel were shown to be related (P < 0.001). The hypothesis that cross-fiber activation enhances notching was confirmed. Retrograde activation did not increase notching nor did ligation of subendocardial fibers.

Additional Indexing Words:

Electrocardiography High frequency cardiac recordings Epicardial mapping

QRS notching High fidelity electrocardiography

The INTEREST in high fidelity electrocardiography is concerned entirely with the fine notches and slurs on the upstroke and downstroke of the QRS complex. These are called high frequency components, since the frequency content is usually higher than can be recorded with conventional equipment. Clinical investigators have been able to show that these notches contain information of value regarding the pathological state of the heart.

Langner and associates⁶ established the presence of notches in patients with other electrocardiographic changes of healed myocardial infarction and noted the serial appearance of high frequency notches in patients with coronary artery disease followed for long periods. The authors⁶ identified high frequency components in patients with cardiomyopathies and systemic sclerosis. Flowers et al.⁷, ⁸ established that ventricular hypertrophy from any cause produced notching. Though many patients with hypertrophy, for instance, those with hypertension, exhibit subendocardial scars, these lesions are by no means common to all kinds of hypertrophy. This important finding pointed to the probability that notching was not caused by the presence of discrete lesions.

In a previous study,⁹ the authors succeeded in artificially producing notching where no notching existed before, by stimulation of the myocardium in such a manner that activation proceeded across, rather than parallel with, the cardiac fibers and in a direction 90° from its normal path. These studies were incidental to a study of the characteristics of electromotive surfaces and were limited to this one angle. It was felt that the hypothesis that cross-fiber activation produces notches had not been fully explored, and that a detailed study using epicardial mapping techniques with greater variation in the angle between fiber direction and the electromotive surface would help resolve the question as to the genesis of notching.

Methods

Dogs were pretreated with morphine sulfate and anesthetized with a combination of Dial-Urethane and pentobarbital. Endotracheal intubation was carried out and respiration maintained with a Harvard respirator.

The electrode system shown in figure 1 was sutured to the left ventricle and the chest closed. This electrode consists of a rotating central disk measuring 1.2 cm in diameter, containing 12 pairs of silver electrodes. Each electrode of the pair was separated by 0.25 mm and insulated with polyester film. The 12 electrodes in the central disk form a rectangle and in use are rotated until two pair of electrodes on the lead edge have synchronous intrinsic deflections. This line-up procedure permits favorable conditions for mapping isochronous lines from the electromotive surface beneath the disk.

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On the outer ring 12 bipolar electrodes are arranged like the hours on a clock. These are used for stimulating wave fronts from 12 possible angles with respect to fiber direction.

Fiber orientation is determined following the study by flattening the ventricular section sewn to the electrodes during fixation with formalin and sectioning four slices at 0.5 mm increments. These sections are marked as to the location of the electrode, stained, and mounted on slides. Figure 2 is an example of one section showing the position of the electrode at the time of study.

All records were made by photographing one sweep of the synchronized trace on a Tektronix D-12 dual beam oscilloscope with a 35 mm camera. A Cherry matrix switch was used to permit rapid switching. Pre-amplifiers were differential high impedance circuits with a frequency response from DC to well over 1000 Hz. The time base, 1000 pips/sec, was introduced onto the second beam of the oscilloscope and photographed with the trace. All records were measured and analyzed by the study of the projected 35 mm slides. A notch was counted when there was a discrete change in direction of the inscribed deflection of less than 5 msec duration. If a second reversal of direction occurred within the 5 msec period, this was counted as the same notch, but if this second reversal occurred later than 5 msec, this was counted as a second notch. The peaks of the R wave and nadir of the S wave were not counted as notches.

Results

Durrer et al. noted notchting in closely spaced bipolar leads when they were not noted in simultaneously recorded unipolar leads utilizing one electrode of the bipolar pair. This raised the question of whether the lead system itself could introduce notchting. It was evident in this study that closely spaced bipolar leads, when oriented so that the lead axis of the electrode pair was parallel with the advancing wave front, would regularly record notched complexes. Rotating the bipolar electrode axis so that it was perpendicular to the wave front eliminated this effect. It was therefore concluded that these notches were artifacts of the recording electrode system. For this reason, closely spaced bipolar leads were never used in these experiments to measure notchting. An example of this type of artificial notchting produced in this manner is shown in figure 3. Bipolar leads in which the electrode spacing was at least 5 mm did not produce this type of notchting regardless of the relationship of the lead axis to the wave front. All leads used to measure notchting were taken from one electrode in the rectangular area to another separated by at least 5 mm. Another lead at right angles to this was also recorded with each change in point of stimulation. The notch counts in these two simultaneously recorded leads were in substantial agreement.

Isoschroons mapping of normal beats provided little information as to the general direction of activation. Normal activation appeared to begin from below upward so that frequently the entire rectangular area would be activated almost simultaneously. In other instances wave fronts would pursue a course which could be identified as parallel with the fibers. Because of the inherent difficulties of drawing conclusions regarding the sequence of normally propagated beats with respect to fiber direction, this approach was abandoned in favor of studying stimulated beats with the ventricle intact and by isolation of the epicardial study site from the subendocardial layer and Purkinje system using the pursestring suture technique described by Watt and associates. This technique permitted cutting through myocardial fibers in the area beneath the electrode and extending 0.5 to 1 cm

Figure 1

The electrode array contains 12 bipolar stimulating electrodes in an outer fixed ring. The rotating disk in the center contains 12 pairs of differential recording electrodes used for isoschroons mapping.

Figure 2

Following each experiment the ventricular muscle studied was flattened during fixation and sectioned at 0.5 mm increments. The original position of the electrode could be reconstructed by marking the tissue with suture and appropriate identifying cuts. It is redrawn to scale here. Fiber direction can easily be identified by the clefts between fibers.
NOTCHING OF QRS

An example of artifactual notching produced when the axis of the differential leads was parallel with the wave front. The upper QRS complex was recorded from electrode 22-21 and the lower QRS complex from 18-17. Stimulation was from S. Fiber direction is shown by parallel straight lines and the isochronous map by curved lines. Artifactual notching was avoided by lining up the axis of differential leads with respect to advancing wave front. This was accomplished by rotating the disk until the intrinsic deflections of two differential leads proximal to the wave front were synchronous. (vertical bar = 10 mV, horizontal bar = 10 msec)

Figure 3

lateral to the electrode array and at a depth which varied between 6 to 8 mm from the epicardium. The upper layer was left intact so that the tissue had a normal blood supply. A blood lake trapped in the ligated muscle prevented propagation of normal beats from below upward. Isolation of this epicardial layer from the subendocardial layer did not produce results that were significantly different in terms of notch count so that data obtained from each were lumped for statistical analysis of the epicardial stimulation data.

In figure 4 the upper panels show normal and stimulated beats before and the lower panels after the

Figure 4

Paired observation before (upper panel) and after (lower panel) cutting all subendocardial fibers beneath the study site. A, B are normal beats; C, D and E, F are stimulated beats recorded while stimulating from different epicardial stimulus sites. All recordings are bipolar leads across the epicardial study site. The time base is 1000 pulses/sec. QRS is altered in the case of normal beats but there was no significant difference in notch count before compared with after this large subendocardial laceration was made. (vertical bar = 10 mV, horizontal bar = 10 msec)
pursestring ligature was pulled. Ligation of these fibers did not contribute to notching of either normal or stimulated beats. Furthermore, if notching was produced prior to the ligation it appeared afterward as well. Panel B compared with panel A is typical of the change in normal beat configuration after the ligature was pulled. The QRS complex is wider, has a different configuration and a single notch appears near the peak of the R wave. A single notch at the peak of the R or nadir of S was noted with equal frequency before and after the ligation.

Panels C and D are examples of stimulated beats before and after ligation of the subendocardial fibers. Since stimulation was produced at the epicardial surface, the subendocardial ligation did not alter the configuration of QRS. There was slight slurring of QRS but no notches prior to ligation and the same result is seen after ligation.

Panels E and F represent stimulated beats across fiber direction. Notches are produced on the upstroke of the R wave before, as well as after the subendocardial ligature was pulled. These experiments and others like them enable us to conclude that removal of all subendocardial fibers beneath the study site altered the direction of normal activation; however, there was no significant difference in notching before and after laceration of these fibers, either with normal or stimulated beats.

Figure 5 illustrates the technique which fairly consistently produced notching of QRS. Stimulation of the point marked S produced activation across the fibers. The parallel lines indicate average fiber direction and the convex lines represent the isosynchronous map derived from differential leads, two of which are shown. In the lower left hand corner the two intrinsic deflections represent the recording from electrode 17-18 and 19-20. In the right hand corner the reference lead is again 17-18 and the other intrinsic deflection is recorded from 8-7. The notched QRS complex in the upper left hand corner was recorded from 16-9.

Figure 6 plots the mean number of notches recorded in the above manner from four animal experiments with the angle between fiber direction and direction of the wave front as determined from isosynchronous maps. This angle is named φ. As the
Correlation of the mean number of notches from all experiments recorded from bipolar leads recorded across the area of study and the direction of activation with respect to fiber orientation. The angle $\phi$ is determined using the fiber orientation in the direction of normal activation as the reference and then measuring clockwise to a vector normal to the isoschronous map. Thus $0^\circ$ and $360^\circ$ represent activation most nearly along the fiber, $180^\circ$ represents retrograde activation, while $90^\circ$ and $270^\circ$ are closest to cross-fiber activation.

angle $\phi$ approaches $90^\circ$ or $270^\circ$, activation is proceeding at right angles to fiber direction whereas as $\phi$ approaches $0^\circ$, $180^\circ$, or $360^\circ$ activation is along the fiber direction. When $\phi$ is greater than $90^\circ$ and less than $270^\circ$, retrograde activation occurs as compared to the direction of normal activation determined from isoschronous maps. Retrograde activation did not increase notching for the equivalent angle $\phi$. It is apparent from figure 6 that activation across the fibers enhances notching compared with activation along the fibers.

To exclude random sampling error, grouped data were used to form a $5 \times 6$ contingency table as shown in table 1. From this the predicted frequency due to random sampling was calculated and the data analyzed by Chi square test to calculate significance. The chance that the frequency distribution shown is due to sampling error is less than 0.01 ($P < 0.001$).

**Discussion**

The mechanism by which notching is produced is unknown. Casella and Taccardi showed that normal cardiac activation had smooth fronts with parallel isoschronous lines usually with no evidence of local delays. In some experiments local lags as high as 50–100 msec were found in unusual circumstances. They concluded that notching was observed only occasionally when the direction of the wave front was oriented parallel to the fibers and propagation was across the fibers. Durrer and associates recorded notching at the site of experimental infarction. Subendocardial infarction showed normal activation time and no notching if the lesion was small. Larger intramural spread of the infarction produced delayed activation time, notching in bipolar but not in unipolar leads. Transmural infarction was associated with lowered voltage, many notches in unipolar leads, and large differences in excitation time within the infarcted area. Abildskov and Boyle produced small subepicardial lesions by injection of formalin and India ink; and though QRS changes occurred, no high frequency notching was observed. Langner and associates, using a similar technique, produced several fine notches and slurring. Fruit, Essex, and Burchell carried out experiments on isolated strips of

**Table 1**

Contingency Table of Observed and Predicted ( ) Notch Distribution

<table>
<thead>
<tr>
<th>$\phi$</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 or more</th>
<th>Row total</th>
</tr>
</thead>
<tbody>
<tr>
<td>$16^\circ - 75^\circ$</td>
<td>9 (8.7)</td>
<td>9 (11.1)</td>
<td>9 (7.5)</td>
<td>6 (5.8)</td>
<td>9 (8.7)</td>
<td>42</td>
</tr>
<tr>
<td>$70^\circ - 135^\circ$</td>
<td>2 (10.6)</td>
<td>0 (13.5)</td>
<td>10 (9.2)</td>
<td>10 (7.1)</td>
<td>20 (10.6)</td>
<td>51</td>
</tr>
<tr>
<td>$130^\circ - 195^\circ$</td>
<td>17 (8.3)</td>
<td>16 (10.6)</td>
<td>4 (7.2)</td>
<td>2 (5.6)</td>
<td>1 (8.3)</td>
<td>40</td>
</tr>
<tr>
<td>$190^\circ - 255^\circ$</td>
<td>10 (7.5)</td>
<td>10 (9.5)</td>
<td>6 (6.5)</td>
<td>7 (5.0)</td>
<td>3 (7.5)</td>
<td>36</td>
</tr>
<tr>
<td>$250^\circ - 315^\circ$</td>
<td>1 (7.5)</td>
<td>8 (9.0)</td>
<td>9 (6.5)</td>
<td>2 (5.0)</td>
<td>16 (7.5)</td>
<td>36</td>
</tr>
<tr>
<td>$310^\circ - 15^\circ$</td>
<td>12 (8.8)</td>
<td>13 (10.6)</td>
<td>6 (7.2)</td>
<td>7 (5.6)</td>
<td>2 (8.3)</td>
<td>40</td>
</tr>
<tr>
<td><strong>Column total</strong></td>
<td>51</td>
<td>65</td>
<td>44</td>
<td>34</td>
<td>51</td>
<td><strong>245 = n</strong></td>
</tr>
</tbody>
</table>

Grouped data are used to form this $5 \times 6$ table describing the mean notch count and direction of propagation with respect to fiber orientation. Chi square was used to evaluate significance of the observed distribution compared to the predicted distribution. The data shown represents four animal experiments. Data before and after the subendocardial ligation are included since no significant difference in notch count before and after this ligation could be found. The differences between predicted and observed notch count with changing direction of propagation was significant at the 0.01 level ($P < 0.001$).
ventricular muscle attached at either end to perfused dog hearts. In one strip the fibers were parallel and in the other the fibers were perpendicular to the long axis of the strip. They showed that activation was delayed by propagation having to course across the muscle fibers as was seen in experimental conditions designed to simulate Purkinje block. It is apparent from examination of figure 10 and figure 11 of their study that cross fiber activation caused marked notching as well as widening of QRS compared to activation along the fibers. This was more apparent after the endocardium which contained parallel fibers was sheared off. These authors did not comment on the notching produced by this experiment, but their results are identical to ours with respect to the conditions producing notching.

The experimental model used in this study was chosen so that both fiber direction and activation sequence could be correlated. It is pertinent to examine whether the notching produced in a bipolar lead on the epicardial surface is recordable in a body surface lead. Direct verification by recording body surface leads was not obtained because of the high noise level in such leads in the open chest experimental animal preparation. The field of study was limited to an area of one square centimeter on the epicardial surface so that it was possible to map isochronous lines of the activation front, and to visualize the fiber direction in pathologic sections. The amplitude of the notches recorded directly across the epicardial surface was 0.1 to 1.5 mV, with occasional notches as high as 5 mV. With the rapid fall-off in high frequency notching with distance, the question arises as to whether such voltages would be recorded in body surface leads using high fidelity techniques.

High fidelity electrocardiography utilizes an expanded time base (500 mm/sec), high sensitivity (0.5 mV/cm) and recording equipment with a linear frequency response to 1000 cps². Records obtained in man using this technique demonstrate that notches measure typically 50 μV (range 10 to 120 μV) and have an estimated equivalent frequency range of 80 to 300 cps. Notching is often limited to less than 10 msec of the total QRS duration. Notching in the experimental animal appears to have the same frequency range as that observed in man. The mean highest voltage of QRS recorded on the dog epicardial surface by the authors² in 85 observations was 62.4 ± 7.2 mV. These voltages were recorded by orientation of a bipolar lead across a propagated excitation wave and represent the optimal conditions for recording. Random voltages recorded on the epicardial surface are more typically 10 to 20 mV and voltages recorded on the dogs body surface are typically 1 to 2 mV. Thus there is a 30- to 5-fold reduction in voltage in the best and worst cases respectively. Thus, notches measuring 1 mV on the epicardial surface might be reduced to 30 μV on the body surface in the worst case, but this is still above the noise level of high fidelity technique and could be resolved. Because of their high frequency it seems unlikely that notches would undergo cancellation.

The fact that a bipolar lead was used seems immaterial since Pruitt and associates¹¹ were able to record notches having similar characteristics with a direct unipolar lead system. From these considerations the authors feel that notches produced in the manner shown would be recorded at the body surface with a suitable recording technique. It is not possible to extrapolate this data further by concluding that disease processes such as transmural infarcts, cardiomyopathies, and ventricular hypertrophy which are associated with notching also have cross-fiber activation. Such a conclusion must await detailed mapping studies in a three-dimensional model. Techniques to carry this out are available, but correlation of this mapping sequence with fiber direction is not possible with existing techniques.

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