Ventricular Quadrigeminy as a Manifestation of Concealed Bigeminy

By Nicholas Kerin, M.D. Isao Mori, M.D., and Matthew N. Levy, M.D.

SUMMARY
Long rhythm strips were analyzed from five patients with frequent ventricular extrasystoles. The predominant pattern was quadrigeminal; i.e., three sinus beats between extrasystoles. However, about 20% of the interectopic intervals contained numbers of sinus beats (S) greater than three. Analysis of the distribution of such values of S > 3 revealed that there were many more odd than even values (P < 0.001). Also, carotid sinus pressure yielded only odd values of S > 3. This predominance of odd values strongly suggested the existence of concealed extrasystoles. Therefore, all odd values of S > 3 were analyzed to determine whether they satisfied the criterion for concealed bigeminy (S = 2n - 1) or for concealed quadrigeminy (S = 4n - 1). The distribution was found to satisfy the criterion for concealed bigeminy, suggesting that the quadrigeminal pattern was a manifestation of a 2:1 rather than a 4:1 block in a re-entry loop. Stable quadrigeminy occurs often in concealed bigeminy, because the re-entrant impulse finds the myocardium excitable after a normal R-R interval but refractory after a compensatory pause.

SCHAMROTH AND MARRIOTT drew attention to a remarkable phenomenon that they observed in long electrocardiograms of certain patients with frequent ventricular premature beats. The intervals between extrasystoles always contained odd numbers of sinus beats; i.e., the number of sinus beats, S, between extrasystoles satisfied the equation S = 2n - 1, where n is any positive integer. They postulated that this pattern of extrasystoles implied an underlying bigeminal tendency, but that many of the extrasystoles were "concealed." These same authors also described cases of concealed trigeminy, where there were 2, 5, 8, 11, etc., sinus beats between extrasystoles; i.e., S = 3n - 1. We have recently proposed that concealed bigeminy and trigeminy are manifestations of a 2:1 and a 3:1 block, respectively, in a re-entry loop; i.e., the coefficient of n in the characteristic equation indicates the block ratio in the re-entry loop.

In the present study, we have analyzed long electrocardiograms from five patients with predominant ventricular quadrigeminy, in whom manifest bigeminal patterns were extremely rare or absent. We have analyzed those portions of the tracings in which S was greater than 3, in order to determine whether the predominant quadrigeminal pattern reflected either concealed bigeminy (S = 2n - 1) or concealed quadrigeminy (S = 4n - 1). Hence, it would be possible to assess whether a 2:1 or a 4:1 block existed in the proposed re-entry loop.

Concealed quadrigeminy has not yet been described in clinical electrocardiograms, to our knowledge. However, concealed trigeminy is well known, as stated above. Also, an electrocardiogram has been called to our attention recently in which the following sequential values of S were observed: 34, 24, 9, 4, 14, 4, 14, 14. This undoubtedly constitutes an example of concealed quintageminy; i.e., S = 5n - 1. Since trigeminy and quintageminy both exist, it may be predicted that concealed quadrigeminy is also a clinical entity. Our analysis of the records from these five patients indicates, however, that the manifest quadrigeminy was actually an expression of concealed bigeminy. Therefore, we have proposed an explanation for the absence of manifest bigeminy and the maintenance of stable quadrigeminy in such patients with underlying concealed bigeminy.

Materials and Methods
Five patients, ranging in age from 42 to 68 years, were evaluated because of frequent ventricular extrasystoles. Electrocardiographic studies included a standard resting electrocardiogram and ten hour Holter magnetic tape recordings. Long strips were analyzed for the distribution of the consecutive numbers of sinus beats between extrasystoles. The records were carefully examined to rule out the possibility of ventricular parasystole. Also the influence of carotid sinus massage was determined in two patients.

Results
Four segments of the rhythm strip from one of the patients are shown in figure 1. In the top segment, the
eight interectopic intervals, each containing three sinus beats, were part of a consecutive sequence of 31 such quadrigeminal periods. As shown in table 1, quadrigeminy characterized 139 of the 175 continuous interectopic intervals analyzed in this patient (case 2). Of the interectopic intervals that did not contain three sinus beats, the numbers of such sinus beats (S) between extrasystoles were predominantly odd. As shown in table 2 (case 2), there were 29 interectopic intervals that contained odd values of S > 3, and only five such intervals that contained even values. On the basis of the binomial distribution, the null hypothesis of an equal distribution of odd and even values of S >

Table 1

<table>
<thead>
<tr>
<th>Number of sinus beats</th>
<th>Bigeminy (B) or quadrigeminy (Q)</th>
<th>Case number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>1 2 3 4 5</td>
</tr>
<tr>
<td>2</td>
<td>B, Q</td>
<td>78 36 172 19</td>
</tr>
<tr>
<td>3</td>
<td>0 3 5 11 4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 2 11 4 5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0 2 11 4 5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0 1 2 10 4 2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1 0 4 1 0 4 2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1 0 4 2 2 4 2 4 4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1 0 2 4 4 2 4 4 4</td>
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<tr>
<td>10</td>
<td>1 0 2 4 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>0 2 4 2 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>0 2 4 2 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>0 2 4 2 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>0 2 4 2 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>0 2 4 2 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>0 2 4 2 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>0 2 4 2 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0 2 4 2 4 2 4 4 4</td>
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<tr>
<td>19</td>
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<td>20</td>
<td>0 2 4 2 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>0 2 4 2 4 2 4 4 4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>102 175 94 203 37</td>
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</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Case number</th>
<th>Odd</th>
<th>Even</th>
<th>P</th>
<th>B</th>
<th>B, Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>4</td>
<td>&lt;0.001</td>
<td>15 4</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
<td>5</td>
<td>&lt;0.001</td>
<td>25 4</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>0</td>
<td>0.001</td>
<td>16 4</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>7</td>
<td>0.25</td>
<td>6 5</td>
<td></td>
</tr>
</tbody>
</table>

The last two columns indicate the breakdown of odd numbers in the second column into those which fit the category of concealed bigeminy (B) alone and those which fit the categories of concealed bigeminy and quadrigeminy (B, Q) together. P represents the probability that the disparity between the number of odd and even values of S, for S > 3, can occur on the basis of chance alone. For all values of S (including S ≤ 3), P < 0.001 for all five patients.
3 was tested. It was found to be highly unlikely ($P < 0.001$) that a ratio of 29:5 (odd:even) would occur by chance alone.

Since the overwhelming majority (170 out of 175) of the values of S in the rhythm strip for this patient were odd, it appeared probable that some form of concealed extrasystoles was present in this patient. The classical variety of concealed bigeminy is characterized by $S = 2n - 1$ sinus beats between extrasystoles; i.e., S may take on all positive odd values. However, other forms of concealed extrasystoles could theoretically also be characterized only by odd values of S, but not by all the odd values. For example, concealed quadrigeminy would be characterized by the equation $S = 4n - 1$; i.e., $S = 3, 7, 11, 15, 19$, etc. These values of S are all odd, but other odd values, such as 1, 5, 9, 13, etc., are not included.

Therefore, concealed bigeminy and quadrigeminy can be distinguished, because half of the odd values of S which earmark the former are not distinctive of the latter. It is evident from figure 1, for example, that values of $S = 1$ and 5 appeared spontaneously and a value of $S = 17$ appeared during application of pressure to the left carotid sinus region. These values typify concealed bigeminy but not concealed quadrigeminy. Figure 2 is a portion of the rhythm strip from another patient (case 3) with a predominant quadrigeminal pattern. Quadrigeminy (top and bottom strips) characterized 86 of the 94 interectopic intervals, as shown in table 1. The top two strips in figure 2 also show an interval for which $S = 19$; this value would be representative of either concealed bigeminy or concealed quadrigeminy. The bottom two strips illustrate the effect of massage of the left
The mechanism responsible for nonparasystolic ventricular premature beats has not been established unequivocally, but the predominant view is that such extrasystoles reflect a re-entry phenomenon. If such an explanation is correct, then a 2:1 block in the re-entry loop would be the most likely basis for concealed bigeminy.

Figure 3 illustrates the postulated course of the cardiac impulse during the sequence of 1, 3, and 5 sinus beats that appears in the second strip of figure 1 (after the initial sequence of seven sinus beats). The normal ventricular activation, represented by R1, is accompanied by a complete traversal of the re-entry loop and a ventricular extrasystole (R2) ensues. An impulse also begins to travel around the re-entry loop after this extrasystole, but it is blocked at some site (B, in fig. 3) in the loop, and so a second extrasystole does not immediately follow the first. After the next normal ventricular activation (R3), an impulse again begins to traverse the loop. It is conducted past B, the site of 2:1 block, and results in another extrasystole (R4). The first two extrasystoles (R2 and R4) in this figure, therefore, are separated by only one normal ventricular activation (R3). Hence, the sequence of R2, R4 constitutes a single interval of manifest bigeminy.

After the second extrasystole (R4) in figure 3, an impulse begins to travel around the re-entry loop, but it is blocked at the 2:1 site, B. The next normal ventricular activation, R5, is accompanied by a re-entrant impulse which progresses past the 2:1 site. However, R5 is not followed by a manifest extrasystole; it is postulated that the impulse is blocked at some other site, C, distal to B. It will become evident that C must be distal to B in the loop, in order that the number of sinus beats, S, will remain odd. The block occurring at C will be called “concealment” to distinguish it from the block occurring at B. The mechanisms believed to be responsible for such concealment will be discussed below. The re-entrant impulse which follows the next normal ventricular activation (R6) is blocked at the 2:1 site. The next re-entrant impulse (after R6) is evidently conducted past both B and C, because an extrasystole (R7) is manifest. Extrasystoles R4 and R7, with the intervening three sinus beats, constitute a manifest quadrigeminal pattern.

In figure 3, there are five sinus beats after extrasystole R4 before another extrasystole becomes manifest. It is postulated that block occurs at site B after activations R6, R10, and R13. A 2:1 block at this site is necessary to account for the occurrence of only odd values of S. Also, “concealment” must occur after R6 and R10, since extrasystoles are not manifest after these activations. The concealment type of block must occur at a site distal to B, or the 2:1 sequence at B would be interrupted and the value of S would no longer always be odd. After activation R13, the re-entrant impulse must have proceeded past sites B and C, because an extrasystole appeared (R4).

A previous study from our laboratory has disclosed one mechanism for the production of “concealment” that is especially important in the genesis of quadrigeminal patterns. It is well known that the refractory period of cardiac cells is dependent on the
length of the cycle preceding the activation.\textsuperscript{15-18} Hence, the compensatory pause must increase the refractory period of the myocardial cells and specialized conducting fibers in the heart.\textsuperscript{16-19} The compensatory pauses after R\textsubscript{4} and R\textsubscript{6} undoubtedly prolonged the refractory periods after normal activations R\textsubscript{a} and R\textsubscript{e}, respectively. No extrasystoles were evident after these sinus beats. It must be presumed, therefore, that the refractory period of some critical element in the re-entry loop must have exceeded the propagation time around the loop after sinus beats R\textsubscript{4} and R\textsubscript{6}.

In figure 3, the compensatory pause which follows R\textsubscript{4} probably also prolonged the refractory period of the cardiac cells after normal activation R\textsubscript{a}. Despite the increased refractory period, the propagation time around the re-entry loop must have been sufficiently long that all cells in the re-entry path, including the terminal myocardial cells, must have been excitable, because an extrasystole (R\textsubscript{4}) ensued.

In the patient (case 2) represented by figures 1 and 3, there were only two instances in which a single sinus beat occurred in an interectopic interval (manifest bigeminy), out of 175 such intervals analyzed. In the other four patients, no such instances of manifest bigeminy (S = 1) were observed. As shown in table 1, the vast majority of interectopic intervals contained three sinus beats; i.e., quadrigeminy was the predominant pattern. Yet based on our analysis of the values of S > 3, the pattern constituted one of concealed bigeminy rather than concealed quadrigeminy. This implies a 2:1 rather than a 4:1 block in the re-entry loop, as shown in figure 3.

If the pattern of extrasystoles in these patients does indeed constitute one of concealed bigeminy, why were manifest bigeminal patterns so rare and manifest quadrigeminal patterns so frequent in these patients? A plausible explanation is suggested from the results of one of our previous studies in experimental animals.\textsuperscript{14} In those experiments, an electrical stimulus was delivered to the left ventricle once every other sinus beat. The coupling interval was progressively varied, and the ratio of sinus beats (SB) to premature beats (PB) was measured. The SB/PB ratio is equivalent to the number of conducted beats between extrasystoles (i.e., to S, as defined above).

The graph of the SB/PB ratio as a function of the coupling interval has a configuration similar to that shown in figure 4. Stimuli delivered at coupling intervals appreciably less than a fall in the effective refractory period of all beats, and produce no premature beats. Coupling intervals approximately equal to a will produce only an occasional extrasystole; if the stimuli are applied only on alternate sinus beats, the numbers of conducted beats will always be odd.\textsuperscript{14} The steepness of the curve in the region of a indicates that a small change in coupling interval will produce a relatively large change in the SB/PB ratio.

At coupling intervals only slightly greater than a, the SB/PB ratio becomes constant at three over a relatively large range of values of the coupling interval. On the graph, this is represented by the plateau from b to c. Over this range of coupling intervals, stimuli delivered every other sinus beat will produce a quadrigeminal pattern. Alternate stimuli will evoke extrasystoles and the remainder will not. Figure 3 illustrates this sequence. The re-entrant impulse after the compensatory pause (e.g., that associated with R\textsubscript{e}) will usually be concealed, because the refractory period is prolonged as a consequence of that pause. Two beats later (R\textsubscript{4}), the refractory period will be shorter, because period R\textsubscript{e}-R\textsubscript{4} (the normal cycle length) is less than period R\textsubscript{a}-R\textsubscript{e} (the compensatory pause). Hence, an impulse traveling around a re-entry loop with a given propagation time is more likely to find the cardiac cells excitable after a normal R-R interval, but refractory after a compensatory pause. Impulses arriving at coupling intervals less than b will usually find the cells refractory even after a normal R-R interval. On the other hand, impulses arriving at coupling intervals greater than c usually encounter excitable cells, even after a compensatory pause. Hence, the length of plateau b-c in figure 4 is a measure of the difference between the refractory period after the compensatory pause and that after a normal R-R interval.\textsuperscript{14}

Re-entrant impulses arriving at any coupling interval from b to c will evoke a quadrigeminal pattern. If the plateau is relatively long, a stable quadrigeminy may be sustained; i.e., random variations in the propagation time around the re-entry loop or in the

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure4.png}
\caption{The ratio of the number of sinus beats (SB) to premature beats (PB), as a function of the coupling interval. The dashed curve represents a shift associated with a change in refractory period.}
\end{figure}
refractory period duration would still be compatible with a stable quadrigeminal pattern. In the electrocardiograms of the five patients analyzed in this study, the long periods with stable quadrigeminal patterns suggest that the coupling intervals must have fallen on such a plateau. Furthermore, numerous instances of SB/PB ratios greater than three were also observed in these five patients, but instances of SB/PB ratios of 1 were observed only rarely. Therefore, it is probable that the coupling intervals must have fallen on a region of plateau b-c that was closer to b than to c, and periodically the coupling interval must have fallen to the left of the plateau.

In figure 4, re-entrant impulses with coupling intervals greater than d would complete the loop after termination of the effective refractory period, even during the beat after a compensatory pause. Hence, all re-entrant impulses, occurring during alternate sinus beats and possessing coupling intervals greater than d would produce a bigeminal rhythm (SB/PB ratio = 1). Coupling interval e represents the normal R-R interval, and hence is the maximum possible coupling interval; impulses with coupling intervals greater than e would arrive at the myocardial cells after they had already been activated by the next sinus impulse. With coupling intervals slightly less than e, fusion beats would occur. Re-entrant impulses with coupling intervals between c and d would arrive when the cells were still refractory after some compensatory pauses, but when the cells were excitable after other compensatory pauses. Hence, with coupling intervals between c and d, the electrocardiogram would contain mixtures of bigeminal and quadrigeminal patterns.14

Changes in the refractory period would produce alterations in the curve of the ratio of SB/PB as a function of the coupling interval. One such alteration is indicated in figure 4 by the dashed curve extending upward from the b-c plateau. Assume, for example, that the continuous curve represents the control conditions and that the dashed curve represents the different refractoriness evoked by carotid sinus pressure (CSP). If the coupling interval happened to be between b and b' the pattern would be one of stable quadrigeminy during the control state. However, if CSP did not appreciably alter the coupling interval but caused the refractory period to shift to that indicated by the dashed curve in the figure, the SB/PB ratio would increase to some number greater than 3; with a 2:1 block in the re-entry loop, that number would be odd. In the electrocardiograms shown in figures 1 and 2, there were no consistent changes in the coupling intervals during CSP, but the SB/PB ratio did increase to a higher odd number. These findings are compatible with the postulated change in refractory period proposed above.

The prompt increase in the SB/PB ratio with CSP in our patients confirms the previous findings of Cope;20 the rapidity of the response strongly suggests a vagal mechanism. Weiss and his collaborators also noted that when cardiac vagal activity was enhanced by operant conditioning techniques31 or by phenylephrine infusions,22 the incidence of ventricular extrasystoles was diminished. Vagal stimulation has also been shown to reduce the frequency of ventricular extrasystoles in experimental animals during ouabain intoxication4 or after coronary artery ligation.3 In the two patients in our study, as the number of sinus beats between extrasystoles increased with CSP, the value of S remained odd. This suggests that the 2:1 block in the re-entry loop was preserved during the increased vagal activity evoked by this maneuver.

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