Mechanism of Ventricular Premature Contraction Showing Interpolated Bigeminy
—Strong Modulation Hypothesis—

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Recent advances in invasive electrocardiology dramatically revealed the unique nature of atrial fibrillation originating from the pulmonary veins. By the same invasive technique, the origin of ventricular premature contraction (VPC) has been clarified as being located in the pulmonary outflow tract, ventricular Purkinje fibers or coronary cusps. Despite these clarifications, the essential mechanism of VPCs still remains uncertain. In addition to automaticity, the possible contribution of reentrant pathway cannot be fully ruled out. To analyze the mechanism, we previously reported on a two dimensional color display of interectopic intervals in VPC patients. This display could estimate the fundamental mechanism of VPC for a full day and clearly differentiate parasystole from fixed coupling interval VPCs.

In this review, first we briefly document the historical background. In order to explain the mechanism of the much more frequently observed fixed coupling interval VPCs, we introduced a new version of color display. Using this modified version, a unique electrocardiogram associated with heart rate doubling during interpolated VPC bigeminy was depicted. The role of interpolated VPCs applied to phase analysis was stressed. From the findings, we developed a strong modulation hypothesis.

Clinical significance of interpolated VPC together with heart rate doubling and harmonic feature was illustrated. Our hypothesis can be applied not only to specific form of parasystole with various coupling intervals but also to fixed coupling interval VPCs. The modified display can roughly discriminate the relative ratio of parasystole cycle length from sinus cycle length. Furthermore, simple estimation of the intrinsic automaticity cycle length together with the heart rate dependence in individual patients was possible.

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Introduction

In Japan, more than 50,000 patients die suddenly every year according to the latest official data. At least 50% of the deaths are due to ventricular fibrillation (Vf). Saving these Vf patients using automated external defibrillators is now possible in
ambulances and public areas with the passage of a new law in 2004, which allows lay by-standers to operate the automated equipment. Vf is the most important target of emergent cardiovascular medicine. A fatal episode of Vf can be induced by a single ventricular premature contraction (VPC); as an initial trigger of Vf, VPC thus plays a major role. However, clinicians are also well aware that an extremely large number of VPCs observed in clinical practice are innocent and not associated with Vf. Efforts to suppress VPCs by antiarrhythmic agents could not improve their prognosis as shown by the CAST study. Instead, ventricular arrhythmia could be controlled by invasive catheter ablation techniques or an internal cardiac defibrillator.

Recent advances in invasive electrocardiology dramatically revealed the unique nature of atrial and ventricular arrhythmias. Atrial fibrillation, for example, has been known to originate from the four pulmonary veins. For suppression, intensive electrical pulmonary vein isolation was developed. The focus of VPC has also been clarified, making ablation possible with a mapping technique targeting the earliest activation site. Despite these clarifications, the essential mechanism of VPCs, especially its clinical patterns including coupling interval and heart rate dependence, still remains uncertain. The aim of this review is to simply document our historical research background and propose a hypothesis concerning the features of VPCs based on the ectopic focus theory using full-day Holter ECG data obtained from our clinic. A simple strategy to clarify their features is presented.

Starting with their experimental study in 1976, Jalife and Moe first proposed the idea of modulated parasystole, which was further demonstrated in clinical cases since 1977. Our clinical research group, traditionally interested in VPCs including parasystole, reported two cases with ventricular parasystole that were studied by incremental atrial pacing in 1979. For the analysis of full-day heart rate dependence of VPCs including parasystole, we proposed a new plotting technique using a computer. Thereafter, a new color display was introduced to subdivide the individual interectopic intervals into bigeminy, trigeminy, quadrigeminy, pentageminy and so on depending on the number of normal QRS. Standard texts prefer to define bigeminy and trigeminy contain two and three normal QRS. We do not use this conventional definition. As a graphic display corresponding to phase response curve (PRC) in experimental study, interectopic interval (I) was plotted against postextrasystolic interval (P) making a full-day postextrasystolic interval vs interectopic interval curve (PIC).

Repetitive interpolated bigeminy with heart rate doubling

Figure 1-A shows ambulatory ECG record obtained from a 72 year-old woman without heart disease. Interpolated bigeminy-type VPCs started at the seventh beat of this record and repeated thereafter. The initial bigeminy interval was 1,048 msec. VPC coupling interval was 376 msec at the beginning and increased gradually to 448 msec. These series of VPCs can be tentatively diagnosed as repetitive interpolated bigeminy. However, this successive form of interpolated bigeminy has rarely been documented.

Interpolated VPCs usually appear during bradycardia. Instantaneous heart rate calculated as 60,000/RR interval (msec) during this record is approximately 60 bpm before VPCs and jumps up to
more than 120 bpm after the repetitive interpolated bigeminy. As far as we know, heart rate doubling of these repetitive VPCs has not yet been reported.

Ladder diagram was displayed under the ECG in Figure 1-A. As has been reported by Katz et al.,\textsuperscript{19)} PQ interval immediately after the initial interpolated VPC was prolonged to 0.22 sec compared with the interval before the VPC. Thereafter, PQ interval continued to prolong until the end of repetitive bigeminy to 0.28 sec. These repetitive interpolated bigeminies appeared frequently and lasted for 10 to 30 seconds in this case. Total VPC counts were 15,752/day.

Ten months after the first record, a second series of ECGs were taken in the ambulatory setting without medication showing an increase in the frequency of VPCs to 40,706/day with alternating interpolated bigeminy and compensatory bigeminy (Figure 1-B). In contrast to the initial record, the second PQ interval after each interpolated VPC was prolonged to 0.23 sec and the third P was blocked as shown in the ladder diagram. Thereafter, VPC appeared immediately in the form of compensatory bigeminy as indicated. The repetitive interpolated bigeminy in panel A was interrupted by the compensatory bigeminy. The role of atrio-ventricular conduction following each VPC was apparent.

Results of full-day VPC analysis were displayed on four panels (A to D) as shown in Figure 2. These uniform displays were also used in Figures 10 and 11. Full-day PIC for the first record in this case was shown in Figure 2-A. Individualized interectopic intervals were plotted against post-extrasystolic intervals (expressed as $X_i-N_i$). Bigeminy intervals were plotted with red circles.\textsuperscript{12,13)} Trigeminy and quadrigeminy intervals were shown with yellow and green circles, respectively. Up to 10 interectopic intervals were illustrated on this panel. Interpolated bigeminy and compensatory bigeminy were plotted on a single regression line, whereas lines for trigeminy and quadrigeminy were not displayed as they could not be plotted on a single straight line. At the left portion of the panel, interpolated VPCs were crowded and dominant.

Figure 2-B displayed histograms of individual interectopic intervals corresponding to bigeminy, trigeminy, quadrigeminy and so on. Sharp lower red peak depicted interpolated bigeminy and red peak just above indicated compensatory bigeminy both showed overlap. Figure 2-C shows histograms of post-extrasystolic intervals subdivided by $n$ with the same color codes. Left sharp red peak corresponded to interpolated bigeminy and right dull red peak to compensatory bigeminy, respectively. Figure 2-D shows our previous plot using mSCL instead of post-extrasystolic interval as abscissa, where the whole bigeminy was located into two clusters. Cluster in the upper left portion with positive slope corresponded to compensatory bigeminy and another flat cluster in lower right to interpolated bigeminy.

Full-day PIC for the second record (not shown) showed the same distribution as in Figure 2-A. Compensatory bigeminy and interpolated trigeminy increased markedly, both of which were clearly depicted on post-extrasystolic interval histogram. From the limited data shown in Figure 1-B, short term (12 minutes) PIC can be obtained, where the slope of the bigeminy regression line was 0.77.
Quite unique and drastic features of these interpolated VPCs were further analyzed in detail. For this purpose, Figure 2-A was further magnified in Figure 3. On this magnified PIC, the three boxes with arrow numbers 1, 2, and 3 indicate, 1) bigeminy intervals with regression line, 2) individual interpolated VPC intervals, and 3) individual compensatory VPC intervals, respectively. Arrow number 4 indicates the y-interception of the bigeminy regression line. The analysis in the next section will use these numbers (1 to 4).

**Features of bigeminy line on PIC**

Bigeminy line indicated by arrow 1 in Figure 3 was further subdivided into interpolated bigeminy and compensatory bigeminity in Figure 4. Panel A shows distribution of interpolated bigeminy (pink dots). Slope of the regression line was 0.709 and y-interception was 603 msec. Panel B depicts distribution of compensatory bigeminy (dark red dots) with a slope of regression line 1.067 and y-interception 358 ms. In panel C, two types of bigeminy were plotted all together without discrimination. The slope of the regression line was 1.035. The two types of bigeminy could not be easily discriminated because of the crowded dots on the line. In panel D, panels A and B were superposed to show the mosaic structure of the bigeminy line. Interpolated bigeminy was mainly observed during a heart rate around 60 bpm, whereas compensatory bigeminy occurred at a heart rate of 60 to 120 bpm.

The average of the slope of bigeminy regression line was $1.044 \pm 0.145$ in our latest 100 successive cases. Very rarely, it exceeded 1.20. It was less than 0.90 in parasystole. In contrast to bigeminy, interpolated trigeminy and compensatory trigeminy were separately plotted on a regression line and both could be easily discriminated as shown in Figure 3. Similar segregated distributions were always observed with quadrigeminy, pentageminy and so on.

To see the heart rate dependence of the two types of bigeminy, heart rate scale for reference was illustrated at the right side of panels A and B. As
shown in Figure 1-A, for heart rate (sinus rate for interpolated bigeminy) calculation, we simply found that the P-P interval without counting VPC during the interpolated bigeminy approximately equaled the interpolated bigeminy interval. Therefore, sinus rate for interpolated bigeminy could be roughly estimated from the bigeminy regression line using the right side ordinate scale. In Figure 4-A, the sinus rate for interpolated bigeminy ranged from 55 to 70 bpm.

Compensatory bigeminy interval contained two sinus beats as shown in Figure 6. Therefore, heart rate for compensatory bigeminy can also be directly estimated from the regression line using the doubled scale, which was twice that of panel A. Heart rate for compensatory bigeminy ranged between 65 to 125 bpm in Figure 4-B.

The properties of the two bigeminy displays in Figure 2 panels A and D were compared using the same portion of the ECG in Figure 1-A as a sample. The abscissa in panel A is obtained from an actually existing post-extrasystolic interval, whereas the abscissa in panel D is the moving average of 8 successive R-R intervals (5 preceding and 3 following R-R intervals; mSCL). This figure is imaginary since the corresponding QRS does not really exist on the ECG. Consequently, a marked dissociation between the figures obtained as mSCL and actual ECG in interpolated VPCs was introduced. The flat portion of the bigeminy interval in panel D, there-
fore corresponded to these interpolated bigeminy. A flat cluster of red dots observed under the positive regression line always suggests the presence of interpolated VPCs.

The heart rate doubling as shown in Figure 1 is quite unique. It is closely related to the atrioventricular (A-V) conduction immediately after VPC. The term tachycardia for this heart rate doubling may not be pertinent. In Figure 1-B, repetitive interpolated bigeminy was interrupted by the subsequent A-V block. We looked further for the mechanism of the co-existence of interpolated bigeminy and compensatory bigeminy. On PIC at this moment, the interpolated bigeminy line and compensatory bigeminy line constituted a single sharp regression line as shown in Figure 3. We can find similar sharp PRCs in experiments corresponding to strong electrical coupling between two pacemakers (ref. 3; their Figure 9). The common features in those PRCs and in our PIC is the most important point we should stress in this article. Based on these findings, we hypothesized that the heart rate doubling was the result of an accelerated focus introduced by strong modulation by the normal QRS in between (strong modulation hypothesis).

Whether this hypothesis applies to all fixed coupling interval VPCs has to be tested in the numerical order given in Figure 3. Findings from clinical laboratories mainly engaged in catheter ablation were also cited. As the reentrant nature of VPC has been questioned for a long time, our findings have to be examined for their clinical applicability. Heart rate doubling could actually occur in atrial tissue or pulmonary veins where the automatic activity was observed. Up until now, no study paid enough attention to the interpolated bigeminy for PRC analysis including parasystoles.6–8)

Features of interpolated VPCs in relation to the interpolated bigeminy (Rule of interpolated bigeminy)

Figures 2-A and 3 showed that interpolated trigeminy and quadrigeminy intervals were approximately equal (or slightly shorter) to two and three times that of interpolated bigeminy shown in Figure 1-A (1,000 msec). This harmonic relation could be extended for n over 7. As far as we know, this relation has been only partly analyzed in interpolated trigeminy.17) To clarify the mechanism of this harmonic relation, interpolated ectopic intervals were superposed in Figure 5. Series of interpolated VPCs corresponding to bigeminy to hexageminy obtained from a continuing ECG strip at the same period were compared using the peak of interpolated VPC as the start line. Trigeminy was precisely analyzed at first, since the result could be extended into quadrigeminy, pentageminy and so on.

In the second panel showing trigeminy, X1-N1 interval (584 msec) was 16 msec longer compared with the interpolated bigeminy in the first panel (568 msec), and consequently, bigeminy was suppressed. As a mechanism, we suspected the following sequence of strong modulation.

1) N1 following VPC-1 could introduce next VPC-2 (Xc: dotted line) but could not excite the ventricle at all because of the refractory period of N1. This could be considered as exit block of the scheduled VPC.

2) Despite this exit block, concealed VPC started next cycle from that point (Xc).

3) Immediately after the concealed excitation, a second normal QRS (N2) occurred on schedule. Xc-N2 was estimated to be 300 msec.

4) This N2 strongly abbreviates or modulates the subsequent cycle (Xc-X3). X2 appears immediately after N2, Xc-X2 was approximately 844 msec, which was much shorter than the bigeminy interval (1.144 msec) in the top panel. Trigeminy interval was thus determined to be 2,008 msec.

Above sequence could be extended into interpolated quadrigeminy and greater as illustrated in Figure 5. If the X2 could not excite the ventricle (exit block), next N3 could occur and strongly modulated X3 will appear with a short coupling interval as quadrigeminy. These sequences are quite similar to the original description of modulated parasystole6) except for the much stronger modulation immediately after the normal QRS, which abbreviates the automaticity up to 50% or more.

Figure 6-A shows another representative PIC recorded in case 2 during medication, where interpolated VPCs were clearly observed at the left side. In Panel B, three interectopic interval histograms were shown. Interpolated VPC intervals in the middle histogram showed the multiples of bigeminy interval (850 msec) as in case 1. From these findings, series of interpolated interectopic intervals can be explained by repetitive concealed interpolated bigeminy associated with single or multiple exit blocks.

Features of compensatory VPCs on PIC

In Figure 7, we tried to analyze the mechanism of compensatory interectopic intervals including trigeminy and quadrigeminy in case 1 in the same manner as shown in Figure 5. Since the compensatory VPC,

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interval ratios in bigeminy, trigeminy, quadrigeminy, pentageminy and hexageminy observed in the same patient as shown in Figure 1. Interpolated trigeminy interval was approximately twice that of interpolated bigeminy. The ratio of interectopic intervals of interpolated bigeminy, trigeminy quadrigeminy, pentageminy and hexageminy was close to 1:2:3:4:5 or multiples of n (n: number of normal QRS between the VPCs; rule of interpolated bigeminy).

According to our strong modulation hypothesis, compensatory trigeminy could be explained as the sum of concealed compensatory bigeminy with exit block and the subsequent strongly modulated bigeminy. This scheme is shown in the second column of Figure 7. We speculate that based on the initial concealed compensatory bigeminy, subsequent concealed interpolated bigeminy could occur repetitively, which brings about compensatory quadrigeminy or pentageminy and so on.

We will try to find the precise PIC features from the distribution patterns of compensatory bigeminy and trigeminy as shown by the arrowed intervals of box 3 in Figure 3. However, approximately two thirds of VPC patients do not show interpolated VPCs at all (Figure 3, box 2). In these groups, we though it would be better to suspend the estimation of their wide range PIC for a while until strong evidence became available.

Fortunately, we learned from our clinical experience that in this group without interpolated VPCs, follow-up ambulatory ECGs occasionally disclosed interpolated VPCs. It mainly depended on depressed A-V conduction immediately after VPC. If the A-V conduction was depressed, interpolated VPCs could be observed and wider range of bigeminy regression could be obtained. For example, anti-arrhythmic agents could occasionally introduce interpolated VPCs as shown in Figure 6 panels C (before) and D (after) for case 3. Elderly patients often show interpolated VPCs at night. If interpolated VPCs could be calculated, their wider range PIC could show the same features as shown in Figure 3.

Patients with slow parastole whose intrinsic cycle length exceeded 2,500 msec were exceptions to this harmonic feature of interpolated VPCs. In these cases, intervals in interpolated VPC may be multiples of interpolated trigeminy interval.

Concerning these mechanisms, recent data during VPC ablation, which looks for the earliest excitation in the ventricle, will be of value. Figure 8, cited from a published article, illustrates an example of compensatory trigeminy with intracardiac electrograms in a case with frequent VPC associated with arrhythmogenic right ventricular dysplasia. Compensatory VPC-1 was preceded by Purkinje potential (marked as P1). Between the VPC-1 and VPC-2, two normal QRS (N1 and N2) were included. A similar Purkinje potential P-2 was seen 295 msec after N1 without ventricular excitation (exit block). P-0 could be found 310 msec after the initial QRS (N0) with exit block. We suspect that concealed compensatory bigeminy (P1-P2) was followed by N2 and thus P3 could introduce VPC-2 resulting in compensatory trigeminy. PIC plotted from these limited points showed a slope of bigeminy regression line 0.95 and y-interception 380 msec, which was compatible with strong modulation.
Distribution patterns in bigeminy and trigeminy in parasystole: standard type and reversed type

In fixed coupling interval VPCs, Nilsson et al. tried to deduce PRC and reported that it could be speculated by the distribution patterns of bigeminy and trigeminy. 21) However, they could not show the corresponding PRC. Recently we reported on the mechanism of distribution patterns in bigeminy and trigeminy in parasystole. 22,23) Standard and reversed distribution patterns were observed in parasystole, which were quite similar to those documented by Nilsson. In the standard pattern, bigeminy appeared during bradycardia and trigeminy becomes dominant during tachycardia. In the reversed distribution pattern, bigeminy appeared during tachycardia and bigeminy is plotted at the left lower portion. Trigeminy is plotted at the longer post-ectopic interval exceeding 1,000 msec. The standard pattern was seen in Figures 2-A.

Those two distribution patterns could be reproduced exactly by computer simulation. Interpolated bigeminy could be simulated by shortening the parameter for refractory period of ectopic focus. 15) Interpolated bigeminy allowed us to extend the scanning zone over the full range of post-extrasystolic interval, especially close to the supernormal zone. This classification can not be applied to slow parasystole, where no bigeminy was observed and trigeminy or quadrigeminy was dominant.

Distribution patterns in bigeminy and trigeminy in fixed coupling interval VPCs

We could apply this classification used for parasystole, especially the reversed pattern, to fixed coupling interval VPCs. A typical example of reversed pattern PIC is shown in Figure 10. Here, in case 5, interpolated VPC was not observed at all. Compensatory bigeminy was plotted at the left lower portion. Trigeminy was plotted at the longer post-ectopic interval exceeding 1,000 msec. The standard pattern was seen in Figures 2-A.
At least four types of trigeminy could exist

We described two types of bigeminy, one interpolated and the other compensatory, both of which were displayed on PIC in Figures 3 and 6. By extending these classifications, at least three types of trigeminy could exist. One is interpolated trigeminy due to repetitive concealed interpolated bigeminy as shown in Figure 5. Another is compensatory trigeminy induced by the sum of concealed compensatory bigeminy and subsequent interpolated bigeminy as shown in Figure 7. The third is trigeminy corresponding to the delay phase of PRC infrequently observed in slow parasystole (cycle length > 2,400 msec) with a sinus cycle length less than half of the parasystole cycle length (< 1,000 msec; not shown).

There is a fourth type of trigeminy as a result of repetitive compensatory bigeminy with a sinus cycle length more than half of the parasystole cycle length. This type was documented as a reversed pattern in our latest paper,[23] and is illustrated in Figures 9 and 10. As for quadrigeminy and pentageminy, more complex types would be expected based on the bigeminy classification and the cycle length ratio.

Figure 7
Compensatory bigeminy, trigeminy quadrigeminy and pentageminy in case 1 as shown in Figure 1. The ratio of interectopic intervals of compensatory bigeminy, trigeminy, quadrigeminy and pentageminy is close to 2:3:4:5 or multiples of (n + 1).

Figure 8
Intracardiac electrocardiogram during the catheter ablation for VPC in arrhythmogenic right ventricular dysplasia; PIC in this case revealed strong modulation. The slope of bigeminy regression line is 0.95 and the y-interception is at 380 msec. Concealed interpolated bigeminy (left) and compensatory trigeminy (right) are shown with intracardiac electrogram. Compensatory trigeminy consisted of concealed compensatory bigeminy with exit block and subsequent interpolated bigeminy (Cited from ref. 20, with permission).
Estimation of the interventricular conduction delay to reach the automaticity focus

From our PIC display, we could always find the y-interception of the bigeminy regression line exceeding 300 msec in almost all patients with fixed coupling interval VPCs as shown by the fourth arrow in Figure 3. In parasystole, it often exceeded 1,000 msec. As a mechanism of the presence of

Figure 9
Panel A: Estimation of intrinsic parasystolic cycle length from PIC in case 4 with reversed pattern. Intercertopic intervals of bigeminy and trigeminy are displayed. Black dots with arrow indicates escape VPC interval plotted on a line $y = x$, which is an intrinsic parasystolic cycle length itself. Panel B: Intercertopic intervals histogram showing bigeminy interval nearly corresponding to the escape VPC interval (arrow). Panel C: ECG showing compensatory trigeminy and subsequent escape beat. VPCs are indicated by arrows. Note that the trigeminy interval is approximately twice that of the escape interval.

Figure 10
Reversed distribution pattern in fixed coupling interval VPCs on PIC (case 5). Four panels are shown in the same style as in Figure 2. Estimation of the interventricular conduction delay to reach the parasystole focus is possible from the PIC (510 msec).
positive y-interception in fixed coupling interval VPCs, we suspect the inter-ventricular conduction delay to reach the ectopic focus and depolarize the membrane potential is a dominant cause. In experimental study, this delay was clearly seen as an electrotonus to fully excite the membrane (ref. 5 Figure 8).

In clinical situations, studies by Ahlfeldt and Nau independently revealed the same feature of PRC without further comments.\(^{14,24}\) This positive y-interception may be considered as a type of entrance block featured by conduction delay (first-degree entrance block). Although this delay has not been fully documented in detail, it can play an important role for PIC analysis. Effect of normal QRS to delay the automaticity could take 300 msec or more. Therefore, QRS with longer post-extrasystolic intervals cannot enter into automaticity focus any more. Computer simulation did not consider this delay at all. Further modification of the model to reproduce the clinical findings will be necessary.

As another way to scan the post-extrasystolic interval and estimate PRC, we extended our analysis to VPCs associated with atrial fibrillation. Traditionally, much research has centered on atrial fibrillation. For example, the famous “rule of bigeminy” concerning the initiation of bigeminy was found by analysis mainly centered on atrial fibrillation by Katz et al. in 1955.\(^{25}\)

Bigeminy distribution in VPCs associated with atrial fibrillation will be of value, since the randomly occurring normal QRS immediately after the VPC can scan the post-extrasystolic interval widely compared with the normal sinus rhythm. Representative PIC in atrial fibrillation (case 6) was shown in Figure 11. In 25 atrial fibrillation patients associated with frequent VPCs, significant bigeminy regression lines were observed in all with slopes of \(1.043 \pm 0.131\) and y-interception values of \(473 \pm 147\) msec. In atrial fibrillation, discrimination of interpolation and compensation was not possible. However, a wider range of post-ectopic interval can be scanned compared with the normal sinus rhythm.

**Estimation of the intrinsic parasystole cycle length from the bigeminy interval histogram**

Until now, intrinsic rate of ectopic focus was documented in a limited study. Watanabe document-
ed a distribution of parasystole cycle length ranging 600 to 2,800 msec in 1973.\textsuperscript{26} A vagal maneuver was applied to introduce escape beats by Nau et al.\textsuperscript{27} In our study, first, we could directly estimate the intrinsic parasystole cycle length from the escape rhythm and bigeminy interval histogram in a limited case with parasystole. Figure 9-A shows PCI in parasystole with escape rhythm (black dot) and Panel B shows escape interval and bigeminy interval histograms, which were found to overlap. In Panel C, ECG showed parasystole cycle length of 1,144 msec. Escape intervals were very close to the bigeminy interval in parasystole. However, they were rarely observed, especially in fixed coupling VPCs.

As a substitutive approach for those major groups without escape rhythm, intrinsic parasystole cycle length was roughly estimated from the PIC and bigeminy interval histogram as shown in Figure 9 panels A and B without considering the diurnal variation. Thereafter, its circadian variations were analyzed in the next section.

Using frequency analysis, Murakawa et al. directly estimated parasystole interval without discriminating interpolated VPCs.\textsuperscript{28} However, the number of simple parasystole patients was limited to less than 10% of total VPC patients. If this analysis was applied to our case 1 as shown in Figure 2-B, a very short basic cycle length of 600 msec, which does not exist on the histogram, could be suspected as a dominant cycle length.

Considering the flexible nature of the ectopic focus as described above with its degree of modulation up to 60%, dominant cycle length of the ectopic focus could be speculated simply from the bigeminy cycle length without modulation or if it exists, with minimum modulation. Therefore, frequency analysis could not be simply applied.

Despite several limitations, we can find the longest compensatory bigeminy interval from the histogram in more than 90% of the patients. Measuring this interval in the clinical setting is reasonable, since it can be obtained instantly from our PIC display. In addition, the longest bigeminy interval can predict the lowest heart rate for compensatory bigeminy. If this value is 2,000 msec, compensatory bigeminy will start to appear at a heart rate 60 bpm. This heart rate can be easily achieved by exercise or by daily activity. In our study, the longest bigeminy interval ranged between 1,200 to 2,700 msec (1,959 ± 296 msec).

The shortest compensatory bigeminy interval is also a useful index. From this value, the heart rate at which bigeminy disappears can be predicted. If this interval is 1,000 msec, bigeminy will go away at a heart rate 120 bpm. Thus, these two compensatory bigeminy intervals have special clinical values.

The shortest interpolated bigeminy interval can be an expression of the strongest degree of modulation. If this interval is 800 msec, interpolated bigeminy will appear at a heart rate of 75 bpm. And if the longest compensatory bigeminy interval of the same patient is 2,000 msec, the degree of modulation is 0.4 (800 msec/2,000 msec). This value, actually cited from case 1, can be considered reasonable since a similar value was observed in experimental studies with strong electrical coupling between two pacemakers.\textsuperscript{51}

To find the intrinsic cycle length more accurately, a wider range of heart rates will be required. A simple technique is to increase the heart rate by exercise. If compensatory bigeminy is induced during exercise at a heart rate above 100 bpm, it can be a marker of relatively fast automaticity with a cycle length of 1,200 msec. On the contrary, if it is induced at a heart rate above 60 bpm, slower automaticity with a cycle length of 2,000 msec is suspected.

Occasionally, complex bigeminy or trigeminy is seen in a single ECG strip (Figure 96 in ref. 17), where they were explained to result from reentry. Another plausible explanation was exit block from the fast ectopic focus.\textsuperscript{29} For example, as the bigeminy interval was 1,600 msec and trigeminy interval was 2,300 msec,\textsuperscript{17} a basic interval of 800 msec was assumed as an intrinsic interval of the ectopic focus. Automaticity of the lower pacemaker in the Purkinje fiber has been believed to be slower than that of the sinus node. We think this fast interval was due to erroneous estimation of the intrinsic interval. A basic interval of 1,600 msec that can be modulated up to 700 msec could be a more reasonable estimation according to our hypothesis.

**Circadian variation in automaticity**

In a previous paper on parasystole,\textsuperscript{11} we documented a circadian variation in parasystole cycle length at approximately ±15%. In fixed coupling interval VPCs, this variation should be also considered. Therefore, during sinus tachycardia, intrinsic automaticity might be more accelerated than the value that can be estimated from the shortening effect of the phase itself on the PRC. This may be the reason why the slope of the bigeminy (especially in case of compensatory bigeminy) occasionally exceeds 1.0 exceed 1.0 as in our latest full-day records (1.044 ± 0.145).
In our study, PIC was precisely analyzed with a short observation period of 0.2 to 2 hours mainly in patients with parasystole or VPC of more than 10,000/day, where the slope of the bigeminy regression line did not exceed 1.0. Since interpolated bigeminy was observed during a period of relative bradycardia, the linearity of the bigeminy regression line should be studied only at the same heart rate in a strict sense. If this method was adopted, information corresponding to the middle portion of PIC would be completely excluded. Consequently, PIC over a wide range could not be estimated.

Considering the diurnal variation, a simple model that can be applied for PIC was illustrated in Figure 12. Classic PRC was shown in panel A. Strong modulation was shown in panel B. Strong modulation with entrance block was shown in panel C. In panel D, diurnal variation of intrinsic cycle length (±15%) and strong modulation with entrance block. Interpolated VPCs could appear only during bradycardia. Blue line indicates compensatory VPCs during short intrinsic cycle length. Exit block was shown with grey line.

In our study, PIC was precisely analyzed with a short observation period of 0.2 to 2 hours mainly in patients with parasystole or VPC of more than 10,000/day, where the slope of the bigeminy regression line did not exceed 1.0. Since interpolated bigeminy was observed during a period of relative bradycardia, the linearity of the bigeminy regression line should be studied only at the same heart rate in a strict sense. If this method was adopted, information corresponding to the middle portion of PIC would be completely excluded. Consequently, PIC over a wide range could not be estimated.

Considering the diurnal variation, a simple model that can be applied for PIC was illustrated in Figure 12. Classic PRC was shown in panel A. Strong modulation was shown in panel B. Strong modulation with entrance block was shown in panel C. In panel D, diurnal variation of ±15% was added and interpolated bigeminy was confined to PIC for bradycardia. Exit block zone was also displayed.

**Definition of heart rate: heart rate doubling or ventricular tachycardia**

As for repetitive interpolated bigeminy, Ikeda predicted theoretically the presence of anti-phasic tachycardia that can rarely occur under limited specific conditions.\(^\text{15}\) Our case shown in Figure 1 might have fulfilled the proposed criteria for this anti-phasic tachycardia. We have to wait for further discussion to decide whether “anti-phase” is a proper description for this case. Similarity of repetitive interpolated bigeminy to high-risk bi-directional ventricular tachycardia should be also considered,\(^\text{30}\) which was frequently observed in catecholamine sensitive ventricular tachycardia.

Repetitive interpolated bigeminy does not require two circuits to induce tachycardia at all, and can actually double the heart rate due to a co-existence of two pacemakers. One pacemaker is the sinus node and the other one is a pacemaker located in a lower portion that can be strongly modulated (up to 50% shortening). Repetitive interpolated bigeminy may be a useful tentative term to explain what is really happening without defining the precise mechanism. Similar VPCs with heart rate doubling was observed in more than 10 patients, in whom we can find association of ventricular tachycardia in at least one third.

**Classification of VPCs based on PIC**

From our study, compensatory and interpolated bigeminy intervals could both reveal an important property in individual patients with frequent VPCs. Compensatory bigeminy intervals roughly corresponded to the intrinsic cycle length of the automaticity. Interpolated bigeminy intervals, if they exist, could be an apparent marker exhibiting the strong degree of modulation. However, considering the presence of exit block as shown in Figures 5 and 7, and first degree of entrance block, a maximum degree of modulation could be much larger than that can be estimated from the shortest interpolated bigeminy interval. Abbreviation of the intrinsic cycle length associated with exit block and not inducing ventricular excitation surely exists as
shown in Figure 8. As for the seriousness of the ventricular arrhythmia, that is whether VPCs with shorter intrinsic cycle length has a worse prognosis, cannot be commented on yet and will require a large-scale organized prospective study for its determination.

As a fundamental mechanism of VPC, a one-dimensional model can be applied by increasing the degree of modulation together with the delay associated with first-degree entrance block. This strong modulation may be affected by the presence of an electrical critical threshold between the focus and normal Purkinje fiber. Damage in the Purkinje fiber would induce electrical uncoupling and ectopic automatic activity at first. As a result, fixed coupling interval VPCs could develop. Further damage could introduce weaker electrical coupling and parasystole with variable coupling interval.

To see the detail of the VPCs, we subdivided VPCs into four categories according to the PIC in Figure 13. First, presence or absence of interpolated VPC was checked on the left side of the PIC. If an interpolated VPC was observed, distribution patterns of bigeminy and trigeminy were compared in the right side of the PIC to divide them into the standard type and reversed type. If an interpolated VPC was not observed, distribution patterns of bigeminy and trigeminy were also examined by the same procedure. Thus, a total of four types could be observed. The actual number of the latest 100 cases with sinus rhythm were also shown. These classifications may be a useful tool to see the details for individual patients. Among many scores obtained in each patient, intrinsic cycle length of VPC seemed to be the most important factor independent of the classifications as a simple index. Maximum degree of modulation can not be obtained in cases without interpolated VPC. The reversed type is an indicator of a shorter intrinsic cycle length of less than 1,500 msec.

In experimental study, effects of extrastimulation on canine ectopic atrial and ventricular tachycardia focus induced by aconitine were studied by Inoue et al. They found abbreviation of automaticity occurred if the center of the focus was prematurely stimulated. Careful comparison with the two-dimensional model including the recent study and our PIC analysis will be necessary.

At any rate, further application of our hypothesis to exercise-induced VPC patients, including aborted sudden death, will be required. Ventricular couplets or triplets were not intensively assessed in our study. For the clarification of supernormal phase in PRC, including the triphasic type, systemic research will be needed. In our findings, PIC corresponding to triphasic PRC was not fully demonstrated since ventricular couplets or triplets were not analyzed.

Summary

We were able to estimate a very sharp PIC by chance from a full-day record showing a unique form of heart rate doubling, from which strong modulation was hypothesized. Strong modulation was induced by frequent interpolated VPCs, which can be seen by slightly depressed atrio-ventricular conduction immediately after VPC. Interectopic intervals in interpolated VPCs showed a multiple of interpolated bigeminy interval due to repetitive exit block. The longest compensatory bigeminy interval is close to the intrinsic ectopic interval. Our strong modulation hypothesis together with clinical observation should be examined in detail to analyze VPC patients that can not show interpolated bigeminy.

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