Fixed Coupling: Different Mechanisms Revealed by Exercise-Induced Changes in Cycle Length

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SUMMARY Fixed coupled ventricular premature depolarizations (VPDs) are usually considered reentrant; recent experimental models have demonstrated that parasystolic rhythms may also appear in fixed coupled patterns. To analyze the mechanisms of fixed coupled VPDs, 60 exercise tests were chosen to evaluate the response of VPD coupling intervals to changes in cycle length of the dominant supraventricular rhythm. Selection criteria included the presence of frequent, unifocal VPDs that were fixed coupled (variation ≤ 80 msec) at any one cycle length, with the persistence of VPDs at several different cycle lengths. Three patterns of response of coupling intervals to changes in cycle length were noted: 1) 32 patients with a direct linear relation (r ≥ 0.9) of coupling intervals to cycle length; 2) 16 patients with coupling intervals fixed, independent of cycle length; and 3) 12 patients with no consistent relation over a wide range of cycle lengths. Two patients in group 2 and four in group 3 fulfilled criteria for parasystole with interectopic intervals that remained constant at different cycle lengths. These results suggest that VPDs in group 1 are reentrant, while some patients with group 2 or 3 responses have evidence for parasystolic rhythms. We conclude that 1) fixed coupling of VPDs is not diagnostic of reentry, and 2) changes in cycle length induced with exercise may be useful in the analysis of mechanisms of VPDs.

FIXED COUPLED VENTRICULAR premature depolarizations (VPDs) are common, and have been considered a marker for reentry.1-3 Recent clinical observations and experimental evidence, however, suggest that parasystolic rhythms may also manifest fixed coupling under suitable conditions.4-6 The present study was undertaken to determine whether changes in heart rate occurring during exercise testing would reveal mechanisms for fixed coupled VPDs not apparent on either resting ECGs or on longer rhythm strips with the usual narrow ranges of heart rates.

Materials and Methods

Exercise tests of 60 patients were selected on the basis of: 1) the presence of frequent unifocal VPDs; 2) fixed coupling of at least three VPDs to preceding supraventricular depolarizations during each of 5 minutes of pre-exercise electrocardiographic recording; and 3) the persistence of frequent VPDs with exercise. Pre-exercise ECG tracings were taken supine, standing and at rest with hyperventilation. Three simultaneous leads (standard lead II, V1 and V6; or V1, V4 and V6) were monitored continuously.

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Definitions

1) Fixed coupling was defined as ≤ 80 msec variation in coupling intervals on initial ECG tracings.
2) Ventricular parasystole was defined as an arrhythmia characterized by:
   A) unifocal ventricular ectopics with interectopic intervals that were multiples of a common denominator
   B) interectopic intervals that were constant (± 5%) or multiples of that constant at different cycle lengths.
3) Intervals were measured as follows:
   A) The coupling interval for each VPD was measured from the earliest inscription of the preceding supraventricular QRS to the onset of the VPD.
   B) QT intervals were determined from cycles uninterrupted by VPDs.
   C) Cycle lengths were measured from the beginnings of successive supraventricular QRS preceding each VPD.

Patient Population

There were 42 males and 18 females. Ages ranged from 18-70 years (mean 51 years ± 12 years, sd). Fifty-three patients were in normal sinus rhythm and seven in atrial fibrillation. Seventeen patients were using digoxin, three propranolol, and seven either quinidine or procainamide. Diagnoses included 15 patients with "chest pain syndromes," 14 with valvular lesions, 13 with ischemic heart disease, eight with idiopathic VPDs and 10 with no cardiac diagnoses. The group with "chest pain syndromes" included patients referred for evaluation of chest pain with either 1) negative exercise test, or 2) normal coronary angiography.
Results

Three patterns of responses in the relationship of coupling intervals to changes in cycle lengths were observed. Patients were designated in group 1, 2, or 3 on the basis of this response: group 1, direct linear relationship of coupling intervals to cycle lengths; group 2, coupling intervals fixed within the same 80 msec, independent of cycle length; group 3, no consistent relationship of coupling intervals to changes in cycle length ("scatter").

There were no clinical features distinguishing patients in any of these groups (table 1). Use of digoxin was comparable in all three groups.

Group 1 (32 Patients)

This response was characterized by a direct linear relationship between decreasing cycle lengths and decreasing coupling intervals throughout exercise over a wide range of cycle lengths. The coefficient of correlation for the coupling interval vs the cycle length was $\geq 0.90$ for all patients in group 1. In addition, for each patient there was never more than 80 msec variation in the coupling intervals for all VPDs occurring at the same cycle length.

The response of a typical group 1 patient is illustrated in figure 1. A graphic demonstration of a typical group 1 response is presented in figure 2.

Group 2 (16 Patients)

ECG recordings from a patient with a typical group 2 response are displayed in figure 3. Although the QT interval decreased with decreasing cycle lengths in a linear manner (coefficient of correlation $= 0.99$), the coupling interval remained fixed throughout exercise (fig. 4). The coefficient of correlation for the coupling interval vs the cycle length was only 0.02. Thus, the coupling interval was independent of both the cycle length and the QT interval over a wide range of cycle lengths.

Group 3 (12 Patients)

This response was defined by fixed coupling at rest but with no consistent relation of coupling intervals to changes in cycle length. This pattern took two forms: 1) In four patients all VPDs at any given cycle length were fixed coupled ($\leq 80$ msec variation). At different cycle lengths the coupling intervals varied, but there was no consistent relation between coupling intervals and cycle length over a wide range of cycle lengths ($r = 0.1-0.7$). 2) In eight patients, although fixed

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Patients with Group 1, 2 and 3 Responses</th>
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<td><strong>Group</strong></td>
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<tr>
<td>-----------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>Total</td>
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*Ventricular couplets, multiform VPDs and ventricular tachycardia.

Abbreviations: FC = New York Heart Association functional classification; IHD = ischemic heart disease; VPDs = ventricular premature depolarizations.
coupling was present on pre-exercise ECGs, coupling intervals became markedly variable with changes in cycle length and fixed coupling was not necessarily observed at any other cycle lengths.

Figure 5 displays a typical group 3 response: coupling intervals did not decrease consistently with decreasing cycle length; nor did they remain fixed (fig. 6).

Five of the 60 patients had previous exercise tests performed from two months to three years earlier. Responses were consistent in each instance.

Evidence for Parasystole

Group 1, 2 and 3 responses were then analyzed for evidence of parasystole. None of the 32 patients in group 1, those with a direct linear relation of coupling intervals to cycle length, met criteria for parasystole. Two of 16 patients in group 2 (fig. 7) and four of 12 patients in group 2 (figs. 8 and 9) fulfilled criteria for parasystole. Each of these patients demonstrated constant interectopic intervals, occurring at multiple cycle lengths during exercise (table 2).

Discussion

Fixed coupling of VPDs to a dominant supraventricular rhythm is commonly observed and has usually been attributed to a reentrant mechanism, while parasystolic rhythms have been considered relatively uncommon.

In the present study we analyzed the exercise tests of 60 patients with frequent unifocal and fixed coupled VPDs on resting ECGs to evaluate the effects of changes in cycle length on fixed coupling. Our results revealed that patients with fixed coupling on resting ECGs have a heterogeneous response of coupling intervals to changes in cycle lengths induced with exercise. This heterogeneity has suggested that multiple mechanisms may be responsible for fixed coupling of VPDs. Three patterns of response were identified. In spite of the variability of response of coupling intervals to decreasing cycle lengths, the QT intervals decreased, as expected, with shortening of cycle lengths in an approximately linear manner in each of these groups. Because this response was uniform for all patients, changes in patterns of coupling could not be explained by differences in QT interval responses.

Of the three responses, group 1 is most consistent with a reentrant mechanism. With decreasing cycle length, there is presumably an associated shortening of refractoriness. This in turn could decrease the conduction time through the reentrant circuit and result in a shortening of the coupling interval.

The group 2 response is more complex. Coupling in-
Intervals remained fixed, independent of cycle length. This pattern of response of coupling intervals to changes in cycle length is not readily explained by previously postulated mechanisms of protection, exit block or intermittency.2, 4, 7, 8, 11 Surawicz and MacDonald, Levy et al., and Schamroth have suggested other electrophysiologic phenomena, including supernormal excitability which may in part explain this pattern of response, but these hypotheses could not be evaluated by our analysis.2, 7, 12, 13

The group 3 response is more readily understood in the context of previous studies of parasystolic rhythms.2, 4, 7-9, 11, 14-18 Four of 12 patients had apparent parasystole revealed by changes in the cycle length of the dominant rhythm. The identification of this subgroup by exercise emphasizes the limitations of previous analyses of VPDs, which were restricted to the relatively narrow ranges of heart rates occurring on long rhythm strips. Fixed coupling on resting ECGs might have precluded this group of patients from being further analyzed for evidence of parasystole. Patients in group 2 and 3 with parasystole were also noted to have frequent fusion beats, characteristic but not necessary, for the diagnosis of parasystole.1, 2, 7, 8, 11 The present study also suggests that a constant interectopic interval (or multiples of that constant) over varying cycle lengths of the dominant rhythm may be useful in the recognition of parasystole.
Pick restudied this concept (called "allorhythms") with the use of artificial pacing. They postulated two electrophysiologic phenomena, each with different mechanisms, that might, under suitable conditions, cause parasystolic rhythms to manifest fixed coupling:

1) Mutual protection of the dominant and parasystolic impulse formation.
   A) fixed coupling due to a simple numerical relation between basic and parasystolic rhythms;
   B) fixed coupling due to a supernormal phase of ventricular excitability.

2) Parasystole with unilateral pacemaker protection or fixed coupling due to "reversed coupling," (i.e., the parasystolic impulse influences the dominant rhythm but not vice versa).

These elegant analyses, however, were limited to observations over narrow ranges of cycle lengths. Langendorf and Pick, as well as Scherf, had recognized the need for longer periods of ECG monitoring and suggested the usefulness of inducing changes in the cycle length of the dominant rhythm with interventions such as exercise, carotid sinus pressure, or pharmacologic agents to unmask possible parasystolic rhythms. Moe et al. have extended this analysis with an experimental succrose gap model. These latter investigators demonstrated that electrotonic influences between a dominant and parasystolic focus can also result in fixed coupling, but only over limited ranges of cycle lengths.

In our analysis, exercise-induced changes in cycle length were useful in unmasking parasystole. Intercpectic intervals that were constant over varying cycle lengths suggested that mutual protection of dominant and parasystolic rhythms was present and accounted for "parasystole with fixed coupling." Further review of our data suggested that additional patients might have parasystolic rhythms. Two patients had interectopic intervals that decreased slightly (e.g., 1300 to 1100 msec) as the cycle length of the dominant rhythm was decreasing markedly (920 to 450 msec) with exercise, possibly related to autonomic effects. Three other patients had interectopic intervals (e.g., 800, 1000, 1200, 2000, 2600 msec) that were calculated to be multiples of smaller intervals that were never directly observed (e.g., 200 msec). In such a case, one could postulate a partially protected or intermittent focus discharging at a rate of 200 msec (300/min). In addition, if one allows for more complex interactions of the dominant and parasystolic rhythms, additional examples of parasystole could be identified. Such complex interactions might explain the group 2 response noted in our study.

No clinical features distinguished patients in any of these groups from one another or from patients with parasystole. As noted in table 1, ventricular couplets, multiform VPDs and ventricular tachycardia were present in all groups, although they were somewhat more prevalent in group 3. None of the seven patients on procainamide or quinidine had a group 2 response.

Parasystole with Fixed Coupling

The concept of parasystolic rhythms manifesting fixed coupling was first suggested in 1917 by the experiments of Kaufmann and Roitherger. They demonstrated that the simultaneous action of two regular pacemakers with different rates might produce repetitive group beating, with recurrence of one or more identical coupling intervals.
FIGURE 6. A representative group 3 response. Coupling intervals (CI: X-X) and QT intervals (●-●) are plotted vs the decreasing cycle lengths. With exercise there was marked "scattering" of coupling intervals but with no direct relation to cycle length (coefficient of correlation 0.35) and no relation to the QT interval, which was again linear (coefficient of correlation of QT interval to cycle length = 0.97).

FIGURE 7. Group 2 response with parasystole. As the cycle length decreased from 730 to 500 msec, the coupling interval remained fixed between 380 and 350 msec. The interectopic interval remained multiples of approximately 1420–1430 msec at rest and throughout exercise.
FIGURE 8. Group 3 response with parasystole. At varying cycle lengths during exercise including 660 and 490 msec, interectopic intervals were constant at multiples of approximately 1620-1640 msec, suggesting parasystole. In contrast to group 2, however, the coupling intervals did not remain fixed; they varied between 510 and 310 msec.

Only two patients with diagnosed parasystole were taking potentially arrhythmogenic agents (one digoxin and one quinidine). Because our selection criteria required frequent VPDs and a persistence of VPDs during exercise, one cannot extrapolate these clinical data to all patients with fixed coupled VPDs on only resting ECGs.

Conclusions
Our data suggest that: 1) fixed coupling of VPDs on resting ECGs may represent heterogeneous electro-physiologic phenomena and can no longer be considered a marker for reentry; 2) changes in cycle length occurring with exercise appear to be useful in elucidating the underlying mechanism of fixed coupling; 3) fixed coupled VPDs with coupling intervals that have a direct linear relation to the cycle length of the dominant rhythm are probably reentrant; 4) ventricular parasystole may be more common than previously suspected, and may be recognized by interectopic intervals that remain multiples of a common denominator over varying cycle lengths.

Table 2. Characteristics of Patients with Ventricular Parasystole

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years, mean ± sd)</th>
<th>Diagnosis</th>
<th>High grade VPDs</th>
<th>FC</th>
<th>Interectopic intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>IHD</td>
<td>MF</td>
<td>III</td>
<td>1420 ± 40 msec</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>Idiopathic VPDs</td>
<td></td>
<td>I</td>
<td>1120 ± 30 msec</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>CP</td>
<td>Couplets</td>
<td>II</td>
<td>490 ± 20 msec</td>
</tr>
<tr>
<td>4*</td>
<td>64</td>
<td>CP</td>
<td>MF, Couplets</td>
<td>II</td>
<td>1620 ± 80 msec</td>
</tr>
<tr>
<td>5†</td>
<td>50</td>
<td>VHD</td>
<td></td>
<td>I</td>
<td>2900 ± 120 msec</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>IHD</td>
<td></td>
<td>I</td>
<td>960 ± 40 msec</td>
</tr>
</tbody>
</table>

*On quinidine at time of study.
†On digoxin at time of study.
Abbreviations: CP = chest pain syndrome; FC = New York Heart Association functional classification; IHD = ischemic heart disease; MF = multiform ventricular premature depolarizations; VHD = valvular heart disease; VPDs = ventricular premature depolarizations.
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FIGURE 9. The ECG tracings of another group 3 patient with probable parasyustole. Again, as the cycle length decreased from 700 to 380 msec, the interectopic intervals remained multiples of 1110 to 1150 msec. Apparent fixed coupling resulted with patterns such as trigeminy and quadrigeminy occurring at certain cycle lengths. At other cycle lengths coupling intervals varied more and were not consistently shorter at shorter cycle lengths. The coefficient of correlation for the coupling intervals vs the cycle lengths for all VPDs in this patient was 0.46.
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