A Cause of Paired Ventricular Extrasystoles

SHINJI KINOSHITA, M.D., KOUSKE FUJITA, M.D., KOUCHI KANDA, M.D., YOSHINORI TANABE, M.D., AND TAKESHI KAWASAKI, M.D.

SUMMARY Eight patients with ventricular extrasystoles were variable in whom coupling intervals of the extrasystoles to the preceding sinus beats were variable and in whom paired ventricular extrasystoles were occasionally seen. In all patients, paired ventricular extrasystoles were initiated only by comparatively late coupled ventricular extrasystoles. However, the interval between the first and the second of these paired extrasystoles was always much shorter than the coupling interval of this first extrasystole to the preceding sinus beat, so that the latter extrasystole often interrupted the T wave of the first one, indicating the R-on-T phenomenon. In two patients there was a gap between the ranges of coupling intervals for single extrasystoles and for the first ones of paired extrasystoles. These observations suggest the presence of longitudinal dissociation in the reentrant pathway as one of the causes of paired ventricular extrasystoles.

CLOSE COUPLED ventricular extrasystoles interrupting the T wave (the R-on-T phenomenon) have been considered to initiate ventricular tachycardia and fibrillation. However, some recent data in acute myocardial infarction have shown that late coupled ventricular extrasystoles also often initiate such ventricular tachycardhythmias. The cause of the latter phenomenon is not known. Therefore, we studied possible causes of paired ventricular extrasystoles. Eight patients with ventricular extrasystoles are reported in whom coupling intervals of the extrasystoles to the preceding beats were variable and paired ventricular extrasystoles were occasionally seen. We investigated the relationship between the coupling interval and the appearance of paired extrasystoles.

Materials and Methods

Electrocardiograms continuously recorded from eight patients were selected because: 1) ventricular extrasystoles with the same configuration were frequently found; 2) coupling intervals of the extrasystoles to the preceding beats of the basic rhythm showed a marked variation of 0.08 second or longer; and 3) in one or more parts of the continuous recording the extrasystoles occurred in pairs. The clinical data of these patients and the lengths of the continuous recordings are presented in table 1. The patients were seen between September 1976 and January 1979. Three of these patients had congenital heart disease and one was studied 6 hours after the onset of an anterior myocardial infarction. The other four patients had no organic heart disease. When electrocardiographic data were obtained (table 1), none of the patients was undergoing digitalis therapy or other antiarrhythmic therapy, though one patient with acute myocardial infarction was administered i.v. lidocaine when short runs of ventricular tachycardia occurred.

All patients were in basic sinus rhythm. Though coupling intervals showed marked variation, no fusion beats were found and we could not discern independence of the ectopic rhythm from the basic rhythm in any part of the recording. Following the classic criteria, the above factors make parasystole unlikely, though these criteria are not always useful in differentiating parasystole from ordinary extrasystolic rhythm.

ECGs were continuously recorded by a direct-recording instrument. All coupling intervals of the extrasystoles were measured by a single observer, and the relationship between the coupling interval and the appearance of paired extrasystoles was investigated. In six patients in whom we saw two or more pairs of extrasystoles in a continuous recording, the difference between the mean coupling interval for single extrasystoles and that for the first ones of paired extrasystoles was statistically analyzed using the t test.

Results

The results are summarized in table 1 and figure 1. We saw a remarkable relationship between the coupling interval to the preceding sinus beat and the appearance of paired ventricular extrasystoles. In all cases paired ventricular extrasystoles were initiated only by comparatively late coupled ventricular extrasystoles. When an extrasystole occurred beyond a certain critical length after the preceding sinus beat, this extrasystole was often followed by another extrasystole. However, when an extrasystole occurred within this critical length after the sinus beat, the extrasystole was never followed by another extrasystole. In all cases this critical length was longer than the middle value between the shortest and the longest coupling interval to the preceding sinus beat. In all of five cases in which three or more pairs of extrasystoles were found in a continuous recording, the mean coupling interval for the first paired extrasystoles was significantly longer than that for single extrasystoles (p < 0.01).

In cases 4–7, when an extrasystole following the sinus beat occurred with a coupling longer than the...
critical length, it always initiated paired extrasystoles. On the other hand, in cases 1, 2, 3 and 8, even when the extrasystole occurred with a coupling longer than the critical length, it sometimes did not initiate paired extrasystoles. In cases 6 and 7, there was a gap between the ranges of coupling intervals for single extrasystoles and for the first ones of paired extrasystoles (fig. 1). Figure 2 shows portions of a recording from case 6. In this case, when the extrasystole was single, its coupling interval was always shorter than 0.48 second (fig. 2, upper strip). On the other hand, when paired extrasystoles occurred, the coupling interval of the first of them was always longer than 0.52 second (fig. 2, lower strip). The extrasystole with a coupling interval between 0.48–0.52 second was never seen.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Organic heart disease</th>
<th>Length of ECG (min)</th>
<th>Ranges of coupling intervals (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58/F</td>
<td>PDA</td>
<td>1</td>
<td>SE: 0.39–0.54, SE1: 0.30–0.54, SE2: 0.40–0.52†, SE3: 0.30–0.34</td>
</tr>
<tr>
<td>2</td>
<td>31/F</td>
<td>no</td>
<td>17</td>
<td>SE: 0.39–0.68, SE1: 0.39–0.68, SE2: 0.64, SE3: 0.50</td>
</tr>
<tr>
<td>3</td>
<td>54/M</td>
<td>no</td>
<td>15</td>
<td>SE: 0.45–0.53, SE1: 0.45–0.53, SE2: 0.52–0.53, SE3: 0.41–0.44</td>
</tr>
<tr>
<td>4</td>
<td>35/M</td>
<td>PS</td>
<td>4</td>
<td>SE: 0.41–0.60, SE1: 0.41–0.50, SE2: 0.51–0.60*, SE3: 0.36–0.40</td>
</tr>
<tr>
<td>5</td>
<td>20/M</td>
<td>no</td>
<td>15</td>
<td>SE: 0.44–0.63, SE1: 0.44–0.56, SE2: 0.63, SE3: 0.38</td>
</tr>
<tr>
<td>6</td>
<td>20/M</td>
<td>no</td>
<td>5</td>
<td>SE: 0.43–0.59, SE1: 0.43–0.47, SE2: 0.53–0.59†, SE3: 0.38–0.46</td>
</tr>
<tr>
<td>7</td>
<td>28/F</td>
<td>ASD</td>
<td>3</td>
<td>SE: 0.40–0.52, SE1: 0.40–0.44, SE2: 0.48–0.52†, SE3: 0.34–0.37</td>
</tr>
<tr>
<td>8</td>
<td>63/M</td>
<td>MI</td>
<td>60</td>
<td>SE: 0.39–0.73, SE1: 0.39–0.73, SE2: 0.57–0.72*, SE3: 0.34–0.48</td>
</tr>
</tbody>
</table>

*p < 0.01, SE1 vs SE2 (unpaired t test).
†p < 0.001, SE1 vs SE2 (unpaired t test).

Abbreviations: SE = interval between the sinus beat and the next extrasystole, regardless of whether the extrasystole was single or paired; SE1 = interval between the sinus beat and the next single extrasystole; SE2 = interval between the sinus beat and the first of the following paired extrasystoles; SE3 = interval between the first and the latter of paired extrasystoles; PDA = patent ductus arteriosus; PS = pulmonary stenosis; ASD = auricular septal defect; MI = myocardial infarction.

**Figure 1.** Relationship of the coupling interval to the preceding sinus beat and the appearance of paired ventricular extrasystoles. Open circles indicate coupling intervals between the sinus beat and the single extrasystole, and solid circles indicate those between the sinus beat and the first of paired extrasystoles.

**Figure 2.** Case 6. Ventricular extrasystoles occasionally occur in pairs. The two strips are not continuous. Coupling intervals of ventricular extrasystoles to the preceding sinus beats are indicated in hundredths of a second.
tricular extrasystoles. The critical coupling interval inducing these paired extrasystoles was about 0.56 second (fig. 1). After that, the ECG was continuously observed with a long-term ECG recording system (Cardilogger, San-Ei Instrument Company, Tokyo, Japan). Figure 3 shows parts of this long recording. When extrasystoles occurred with couplings longer than the critical length of 0.56 second, they often initiated short runs of ventricular tachycardia. Case 5 also had occasional tachycardia that continued for a minute, though the ECG during the attack could not be taken. The other patients had no tachycardia.

**Discussion**

**Mechanism of Paired Extrasystoles**

The above observations in this study suggest a cause for paired ventricular extrasystoles (figs. 4 and 5). The explanations we discuss are valid regardless of whether the conduction disturbance occurs in the reentrant pathway or in the junction between an ectopic focus and the surrounding ventricular myocardium. However, in this study, the explanations are made only with regard to the reentrant pathway, because we believe that such ventricular extrasystoles with variable coupling are caused by the reentrant mechanism.\(^\text{14, 17}\)

Figure 4 shows part of the recording in case 1. In this figure the sinus beat S\(_1\) is followed by the extrasystole E\(_3\) with a comparatively short coupling of 0.40 second. The sinus beat S\(_2\) is followed by the extrasystole E\(_4\) with a comparatively long coupling of 0.48 second. The next sinus impulse, S\(_n\), is not conducted to the ventricles; it is blocked at the atrioventricular (AV) junction. After that, the sinus beat S\(_7\) is not followed by a manifest extrasystole, suggesting that an event similar to the Wenckebach phenomenon occurs in the reentrant pathway; in this case, however, a block subsequent to the progressively increasing conduction delay occurs at the AV junction. The diagram below the strip shows that after the progressively increasing conduction delay in the reentrant pathway, a block of the sinus impulse (S\(_n\)) occurs at the AV junction and, in the subsequent sinus impulse, S\(_7\), conduction in the reentrant pathway recovers. Because of insufficient conduction delay, the sinus impulse S\(_7\) becomes a concealed ventricular extrasystole due to interference at the distal end of the reentrant pathway.\(^\text{18}\) Figures 5A and B illustrate such concealed and manifest reentrant extrasystoles. The upper end of the illustrated reentrant pathway indicates the distal end of the pathway at which unidirectional block occurs. The impulse can enter the reentrant pathway only through the lower end of the illustrated pathway.

In the lower strip of figure 4, the sinus beat S\(_{15}\) is followed by the extrasystole E\(_{12}\) with a coupling of 0.42 second. The sinus beat S\(_{16}\) is followed by no manifest extrasystole, suggesting that this sinus impulse is blocked at the reentrant pathway. However, the next sinus beat, S\(_{17}\), is followed by the extrasystole E\(_{14}\), with a comparatively long coupling of 0.47 sec-
ond. This finding suggests that after the sinus impulse $S_n$ invades a considerably large part of the reentrant pathway, it becomes a concealed ventricular extrasystole due to exit block within the reentrant pathway.\textsuperscript{18, 19} Figure 5C illustrates such a concealed extrasystole. El-Sherif et al.\textsuperscript{20} recently demonstrated the presence of manifest and concealed reentrant ventricular extrasystoles in the late myocardial infarction period in dogs.

The findings shown in figure 4 indicate that the absolute refractory period at a distal level of the reentrant pathway is about equal to or slightly longer than the sinus cycle length in this figure. In the upper strip, after conduction in the reentrant pathway recovers in the sinus impulse $S_n$, conduction delay in the pathway again increases. After marked delay in the pathway, the sinus impulse $S_n$ reenters the ventricles and becomes the extrasystole $E_t$. The coupling interval of the extrasystole $E_t$ to the sinus beat $S_n$ (0.50 second) is markedly prolonged but still much shorter than the sinus cycle length. This indicates that the interval $S_nE_t$ is much shorter than the absolute refractory period at the distal level of the reentrant pathway. Despite this, the extrasystole $E_t$ is followed by another extrasystole, $E_n$. If the extrasystole $E_t$ occurred after the sinus impulse $S_n$ stimulated all the parts of the reentrant pathway, the extrasystolic impulse $E_t$ could not pass again through the pathway, and the extrasystole $E_t$ would not occur. Therefore, we must assume that the sinus impulse $S_n$ does not stimulate all the parts of the pathway; that is, that the extrasystole $E_t$ occurs after the sinus impulse $S_n$ passes through only a part of the pathway. Longitudinal dissociation in the reentrant pathway is strongly suggested. Paired ventricular extrasystoles $E_{17}$ and $E_{18}$ in the lower strip also suggest such longitudinal dissociation.

Diagram $D_1$ in figure 5 illustrates longitudinal dissociation in the reentrant pathway, in which the absolute refractory period of one lateral part (the left side) is slightly longer than that of the other lateral part (the right side), and the sinus impulse passes through the right side only. Thereafter, it becomes a manifest extrasystole with a prolonged coupling.

Diagram $D_2$ illustrates the stage after diagram $D_1$. In this stage the left side of the reentrant pathway recovers from the absolute refractory phase. Diagram $D_3$ shows that after the extrasystolic impulse becomes manifest in diagram $D_1$, it reaches the reentrant pathway again and, passing through the left side of the pathway, becomes another manifest extrasystole. In diagram $D_3$ the impulse falls considerably after the absolute refractory period of the left side, and therefore reaches the distal end of the pathway after a comparatively short conduction time. As a result, the latter of paired extrasystoles occasionally interrupts the T wave of the first one, indicating the R-on-T phenomenon.

In case 2 ventricular extrasystoles usually showed concealed bigeminal rhythm. This rhythm suggests 2:1 exit block due to the long absolute refractory period in the reentrant pathway.\textsuperscript{18, 20} This period in case 2 was considered to be about 0.85 second, which
was much longer than the coupling interval of the first of paired extrasystoles (0.64 second). As in case 1, this suggests longitudinal dissociation in the reentrant pathway.

A discontinuous AV nodal conduction curve during the atrial extrastimulus examination suggests dual AV nodal pathways.21 As in figure 5, if there is some difference not only in the absolute refractory period, but also in the conduction velocity between the right and left sides of the reentrant pathway, and if the conduction velocity in the right side is slower than that in the left side, the discontinuity as seen in the AV nodal conduction will also occur in conduction in the reentrant pathway. A gap will be found between the range of coupling intervals shown in the stage of diagram B and that in the stage of diagram D₁. Actually, such a gap was found in cases 6 and 7 (fig. 1). This reinforces the presence of longitudinal dissociation in the reentrant pathway.

In the other four cases, neither the presence of such a gap between the ranges of coupling intervals nor the presence of concealed extrasystolic rhythm could be disclosed. However, the fact that paired extrasystoles were initiated only by comparatively late coupled extrasystoles suggests that in these cases too, longitudinal dissociation in the reentrant pathway might be the cause of paired extrasystoles. In these four cases the interval between paired extrasystoles E₁ and E₂ was much shorter than the interval between the preceding sinus beat S and the extrasystole E₁; the difference between them was markedly long. If the extrasystoles E₁ and E₂ were caused by reentry using the same pathway, the markedly long difference would indicate that the impulse S could not reach the entrance of this reentrant pathway without passing through a region showing abnormally prolonged conduction delay, but that the impulse E₁ could reach the same entrance without passing through this region. The above assumption also indicates that a form of dual pathways was present as a cause of paired ventricular extrasystoles. Some recent data in animal experiments suggests that longitudinal dissociation occurs in the intraventricular conduction system.22 25

In figure 5, if the conduction time in the left side of diagram D₂ shortens further, the impulse will become a concealed extrasystole due to interference at the distal end of the pathway. Diagram D₃ shows such a state. This might explain some of the single extrasystoles with long couplings in cases 1, 2, 3 and 8, in whom even when an extrasystole occurred beyond the critical length after the sinus beat, it sometimes failed to initiate paired extrasystoles.
Relationship to Initiation of Ventricular Tachycardia and Fibrillation

The patient with acute myocardial infarction (case 8) showed short runs of ventricular tachycardia. In all of the other cases, an ECG showing ventricular tachycardia could not be obtained. Therefore, we cannot discuss general mechanisms that cause ventricular tachycardia and fibrillation initiated by late coupled ventricular extrasystoles in acute myocardial infarction. However, these observations for paired extrasystoles suggest the possibility that in some patients with acute myocardial infarction, similar longitudinal dissociation in the reentrant pathway might occur during the initiation of ventricular tachyarrhythmias. In recent animal experiments, El-Sherif et al., 26 showed functional dissociation of conduction in the infarction zone. An explanation for initiation of ventricular tachyarrhythmias is discussed below.

Diagram D2 in figure 5 illustrates the stage after diagram D2. Diagram D3 shows that after the extrasystolic impulse becomes manifest (diagram D3.), it usually cannot reenter the pathway through either side, because the conduction time in the left side at the stage of diagram D2 is comparatively short. This may be why, in usual cases of paired ventricular extrasystoles, ventricular tachycardia does not occur. However, if such paired extrasystoles originate in the infarction zone with its increased vulnerability, ventricular fibrillation or tachycardia with a considerably rapid rate may be initiated by the latter of paired extrasystoles (diagram D3), which is closely coupled to the first one. The reentrant circuit for such tachyarrhythmia with a rapid rate is probably different from the reentrant pathway for paired extrasystoles; the circuit may be located in the region adjacent to the distal end of the pathway for paired extrasystoles.

Diagram D3 shows that if, alternatively, the manifested extrasystolic impulse in diagram D3 can reenter the pathway through the right side, it will become a third manifest extrasystole, and a ventricular rhythm will be initiated and maintained for some time; however, the rate of this ventricular rhythm may be relatively slow because of the long absolute refractory period in the pathway.

Our observations suggest that in some patients with ventricular tachycardia or fibrillation, dual reentrant pathways due to longitudinal dissociation may initiate the tachyarrhythmias, although most patients with ventricular tachyarrhythmias do not have such dual pathways. In fact, in many animal and clinical cases of El-Sherif et al. 27 and Wellens et al. 28, 29 electrically induced ventricular tachycardia can be explained by the same reentrant pathway. However, the reentrant mechanism using the same reentrant pathway cannot explain the fact that ventricular tachycardia or paired extrasystoles were initiated only by late coupled ventricular extrasystoles.

References

15. Kinoshita S: Concealed ventricular extrasystoles due to interference and due to exit block. Circulation 52: 230, 1975
Sudden, Unexpected Death in Avid Dieters Using the Liquid-Protein-Modified-Fast Diet

Observations in 17 Patients and the Role of the Prolonged QT Interval

JEFFREY M. ISNER, M.D., HAROLD E. SOURS, M.D., ALLEN L. PARIS, M.D., VICTOR J. FERRANS, M.D., AND WILLIAM C. ROBERTS, M.D.

SUMMARY Clinical and morphologic findings are described in 17 patients who died suddenly and unexpectedly during or shortly after use of the liquid-protein-modified-fast diet. Of the 17 patients, 16 were women, most were young (average age 37 years), and most lost a massive amount of weight (average 41 kg or 35% of their prediet weight) over a short period of time (average 5 months). Eight had one or more episodes of syncope. Multiple-lead ECGs were recorded in 10 patients. All had normal sinus rhythm; all had episodes of ventricular tachycardia; nine and possibly 10 patients had prolongation of the QT interval, unassociated with the recognized causes of QT interval prolongation in at least seven of the nine patients; and nine had diminished amplitude of the QRS complexes ("low voltage"). Histologic study of left ventricular myocardium in 14 patients disclosed attenuated myocardial fibers in 12, increased lipofuscin pigment in 11, and mononuclear-cell myocarditis in one. Similar histologic findings, however, also were found in 16 cachectic control subjects studied in similar fashion, but ECGs in them showed no prolongation of QT intervals or episodes of ventricular tachycardia. Thus, semistarvation, particularly in the face of antecedent obesity, is a cause of acquired QT interval prolongation, and repeated ECGs are recommended in patients on semistarvation diets for treatment of obesity.

In 1976 a book entitled The Last Chance Diet was published and almost immediately, several liquid-protein-modified-fast (LPMF) diets became very popular and fashionable as means of rapid weight reduction. These diets were intended to serve as the dieter's only source of calories. Between January 1, 1977 and December 31, 1977, it was estimated that more than 100,000 persons had used one or more of the LPMF diets as their sole source of nourishment for at least 1 month. By August 1977, however, sudden death in several young LPMF diet users was reported to either the Food and Drug Administration (FDA) or the Center for Disease Control (CDC), and between July 1977 and January 1978 at least 60 deaths among avid users of the LPMF diet were reported to the FDA and CDC. In 28 of these 60 patients, there was clinical or necropsy evidence of an underlying disorder that may have contributed to the patient's death, and in 15 other patients information regarding the circumstances of death was incomplete. This report focuses on the other 17 patients who before LPMF dieting were healthy and in whom detailed clinical and/or necropsy information was available. Attention is called to a poorly documented cause of QT interval prolongation and sudden death.

Patients

Certain clinical and morphologic findings in the 17 patients are summarized in table 1. Patients 3 and 5, 8, 9, and 10 have been reported by other investigators. Symptoms attributable to cardiac dysfunction were minimal to absent in all 17 patients. None had evidence of congestive cardiac failure. Only four patients (6, 9, 11 and 12) (table 1) had evidence of systemic hypertension at some time. Death was sudden and occurred outside the hospital in six patients. Of the other 11 patients, eight presented with syncope and subsequently died in the hospital; the other three were comatose upon admission to the hospital and each died soon thereafter.
A cause of paired ventricular extrasystoles.
S Kinoshita, K Fujita, K Kanda, Y Tanabe and T Kawasaki

Circulation. 1979;60:1395-1401
doi: 10.1161/01.CIR.60.6.1395

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1979 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/60/6/1395