Factors Influencing the Time of Appearance of Premature Systoles (Including a Demonstration of Cases with Ventricular Premature Systoles due to Re-entry but Exhibiting Variable Coupling)

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The genesis of the most common cardiac arrhythmia, that due to premature systoles, still remains obscure. Observations made upon two patients with ventricular premature systoles are reported because of some unusual features of their timing which shed some light upon the mechanism behind the appearance of premature systoles, regardless of the extrasystolic impulse. The theories of the extrasystolic irregularities are reviewed with particular attention to the criterion of "fixed coupling" generally used to distinguish between premature systoles explained by a re-entry mechanism and those explained by a parasystolic pacemaker.

In most studies of premature systoles, the time of their appearance has been almost entirely ascribed to the mode of origin of the ectopic impulse. In fact, the distinction between the re-entry mechanism in cases of premature systoles with fixed coupling and parasystole in cases with varying coupling and with a common divisor of all interextrasystolic intervals was based primarily on such time relations. This article will attempt to demonstrate that variations in conduction of the premature impulse constitute another factor which determines the time of appearance of premature systoles; thus, in the 2 cases to be described, the premature systoles can be ascribed to a re-entry mechanism and their varying coupling explained by varying conduction. Rothberger emphasized that fixed coupling of premature systoles did not rule out the possibility of a parasystolic mechanism;

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Our material is presented to demonstrate that varying coupling of premature systoles does not rule out the possibility of a re-entry mechanism.

Mode of Origin of Premature Systoles

The genesis of premature systoles has been the subject of much study. Most observers now feel that premature systoles may arise in various ways.

The concept of parasystole as first suggested by Fleming,1 and later stated definitely by Kaufmann and Rothberger,2-4 has as its basis the idea that certain premature systoles were manifestations of an ectopic focus with a regular rate of impulse formation. Protection block (Schutzblocierung) was postulated to account for the fact that this ectopic center was apparently not penetrated by impulses of the dominant rhythm and discharged, with a disruption of its intrinsic rhythm.3-6 The frequency and time of appearance of the premature systole were thought to depend on interference and dissociation between the two rhythms, on the presence of exit block (Austrittsblockierung),5-7 and possibly also on some effect of the dominant rhythm on the "strength" of impulse formation in the ectopic focus.8 Ventricular premature systoles which have been shown to be produced by such a mechanism...
usually do not show fixed coupling with the dominant beats. Occasionally, however, fixed coupling may appear to be present when only a short strip of record is available because of a fortuitous relationship between the parasystolic rhythm and the dominant rhythm (e.g., when the cycle length of the dominant rhythm is almost an exact multiple or divisor of that of the ectopic rhythm). A parallel situation may be seen occasionally in complete atriocentrical block in which the sinus nodal rate is almost exactly twice the idioventricular rate; short strips of record may then appear to demonstrate partial A-V block with 2:1 conduction, and only when a longer strip is examined is it seen that the two rhythms are almost completely independent.*

However, most premature systoles cannot be explained by the above concept since they usually demonstrate fixed coupling to the beats of the dominant rhythm, regardless of variations in this dominant rhythm. In such cases, most investigators are convinced that the impulse causing the premature systole is in some way itself caused by the beat that precedes it.6,9 The exact nature of this causal relationship is still poorly understood.

Many investigators have felt that the underlying mechanism for this type of premature systole is re-entry, and that the premature beat is actually caused by the same impulse which produced the beat of the dominant rhythm but which, because of a certain critical prolongation of the refractory period in some region of the heart, is able to re-enter the heart and so cause the premature systole. Attempts were first made to explain these premature systoles on the basis of a circus movement.9-11 However, the fact that the coupling may be sometimes as long as 0.85 second 5,6,12 has been considered to be an important argument against this circus movement theory. For this reason, other investigators have suggested a broader concept of re-entry as a possible physiologic mechanism. They feel that in a certain region of the heart there may exist a critical prolongation of the refractory period so that the normal impulse, when it first arrives at this area, cannot penetrate or is not conducted through. When, however, very shortly afterwards the impulse reaches this area by another route, its refractory period will now be over and this impulse may then penetrate and be conducted through. In passing out of this area this impulse may now restimulate the rest of the heart provided the refractory period of the latter is now over.6,9,13 In any discussion involving this region, the separate conception of protection block is unnecessary since the prolonged conduction assumed to be present in this region may tend to have the same effect as entry block.

Other observers, avoiding this concept of re-entry, believe that the premature systole originates as a new stimulus from an ectopic or heterogenetic focus which was in some way activated by the preceding beat. Scherf14 experimentally, by injection of various drugs into the heart muscle, produced ventricular premature systoles of constant contour which showed fixed coupling to the preceding beats. That each premature systole was induced by the preceding sinus impulse was shown by the fact that the premature systoles disappeared when sinus standstill was produced by vagus stimulation. He believed that these premature systoles were not due to a re-entry mechanism, but were due to the formation of a new stimulus, because warming the area of injection increased the number of existing premature systoles or elicited premature systoles if tried shortly after they had disappeared. In earlier experiments15 when premature ventricular systoles produced in such a way followed not only the sinus beats but also artificially stimulated beats, he observed that these ventricular premature systoles retained their original contour. The coupling to the artificially stimulated beat would depend on where in the heart this artificially stimulated beat was produced, and whether or not either or both bundle branches

*Segers and associates* have shown that even during complete A-V block there may be some synchronization of auricular and ventricular rhythms, or frequent close association of a P' and R wave (phénomène d'accrochage). They attributed this to interactions developing between ventricles and auricles, without any conduction pathway, similar to the synchronization which may occur when two frog hearts are placed in contact with each other.
were intact. If the artificially stimulated beat arose in the opposite ventricle the coupling to the premature systole would be longer than when it arose in the same ventricle as the premature systole. The fact that the ventricular premature systoles retained their original contour, he felt, argued conclusively for the idea that these ventricular premature systoles arose from one sharply circumscribed area and this, according to him, spoke against re-entry. However, if one postulates that the subepicardial injection of strophanthin, or digitoxin, produced a localized area of prolonged conductivity (as these drugs are known to do) where the re-entry phenomenon could occur, then certainly heating this area could have the effects he discovered. Because this area remained in the same location, the impulse coming out of this area would be conducted through the heart along the same pathway, and the form of the ventricular premature systole would thus remain constant.

Many of those who feel that premature systoles with fixed coupling originate in an ectopic focus believe that the activity of the ectopic center although continuous is raised to an effective level only when an impulse is conducted into it, or is completely inactive and develops a new impulse only when a stimulus penetrates it. The idea of an ectopic center which rhythmically discharges subliminal impulses which are not effective, or cannot get out of the center, thus is not very far removed from the concept of parasystole. Indeed, cases have been reported in which the ventricular premature systoles were at first clearly parasystolic in origin, and in later records appear with fixed coupling, and another reported in which ventricular premature systoles with fixed coupling and others due to parasystole were present in one record.

It may well be asked: What happens to a sinus impulse which has activated the ectopic focus during the interval between the normal beat and the premature systole? If the length of the coupling interval is a measure of slow conduction out of the ectopic focus to the ventricle, then why is it necessary to postulate an ectopic focus, and how can we say the stimulus is one that has just been generated and not the same one that has re-entered the ventricle? Attempts to answer this question have been made by suggesting that it is not the sinus impulse itself that activates the sinus node but makes possible the egress of the impulse from this center into the rest of the heart, but some condition produced by this sinus impulse which becomes effective only sometime after this sinus impulse has passed. Thus, Rothberger mentions that the normal or dominant impulse may have an effect on the conduction out of the ectopic center similar to the Bahnhof effect of von Skramlik (path-clearing effect of a nodal beat for subsequent A-V conduction). Rothberger also suggests the possibility that an impulse can come out of the ectopic center only during the supernormal phase of conductivity produced by the preceding sinus beat. Segers emphasizes the role of the negative after-potential in the genesis of premature systoles, and he feels that the hyperexcitability after each contraction which coincides with the negative after-potential is responsible for the excitation to activity of an ectopic center. He found experimentally that drugs which diminish the negative after-potential lead to the disappearance of premature systoles (acetylcholine, quinidine, cocaine, procaine) and drugs which increase the negative after-potential increase the frequency of premature systoles (epinephrine, digitalis, strophanthin, veratrine, aconitine). However, the presence of very long coupling (e.g., 0.85 second) cannot be explained by the above theories since the supernormal phase of recovery or the negative after-potential usually does not appear so late in diastole. The presence of long coupling, however, would not exclude the application of any of these factors to an area of prolonged conduction (where re-entry occurs), and where they could facilitate the entry or exit of an impulse.

The presence of this interval between the beat of the dominant rhythm and the premature systole has also been used as an argument against re-entry since during this interval there is no evidence in the electrocardiogram of the slowly traveling impulse in the re-entry pathway. However, a wave of excitation of narrow front and of very slow velocity will not register
in the electrocardiogram. This can be seen in the portion of the electrocardiogram in which A-V conduction and conduction down the common bundle and bundle branches occur, and in which no sign of such activity can be detected.

Thus, in summary, it may be stated that most investigators agree that in the case of ventricular premature systoles with fixed coupling, the impulse of the dominant rhythm in some way causes the emission of another impulse from a relatively fixed focus. Whether this focus is an area in which conduction is prolonged so that re-entry becomes possible, or whether this focus actually becomes activated to initiate a new impulse cannot be answered definitely at this time.

**Variable Conduction and Premature Systoles**

In any attempt to determine the mechanism responsible for premature systoles in a given case, a consideration of the variations in coupling of the premature systoles to the dominant beats, and of the variations in intervals between the premature systoles, is of extreme importance. However, there is a factor influencing these critical time intervals which has been somewhat neglected in most discussions. The impulse which is responsible for the premature systole must be conducted along pathways in which variations of conduction will have a marked effect on these time relationships. Three possible regions may be considered where variations may occur in the conduction of the impulse which causes the premature systole: (1) In the pathway of the impulse of the dominant rhythm to the ectopic focus or to the region where re-entry occurs. (2) In the pathway from the point of exit from this ectopic focus or area of re-entry to the rest of the heart. This factor is important also in cases of parasystole. (3) In a region which is somewhere between the above two pathways, a region where there exists impaired conduction making the phenomenon of re-entry possible, namely, the re-entry pathway itself. All of the physiologic factors which influence conduction anywhere in the heart can affect conduction in any of these pathways.

If the rates of conduction along all of the pathways outlined above remain constant their existence will not interfere much with our attempts to understand the origin of the premature systoles in any given case. However, when such conduction delays become variable, the unravelling of the genesis of premature systoles in certain cases becomes very difficult. Thus, in a given case in which a regularly discharging parasystolic focus may be responsible for the premature systoles, the proof of such a mechanism may be greatly complicated or impossible, when the intervals between the premature systoles are affected by variable conduction in the second pathway described above; it will then be impossible to find a common divisor for the various intervals between the premature systoles. Such factors may be responsible for the variations in interextrasystolic intervals in the cases reported by Iliescu and Sebastiani. A similar situation holds in partial A-V block with the Wenckebach phenomenon and with dropped beats, in which, although the rate of discharge of the sinoauricular node is absolutely regular, the ventricular rate may be quite irregular because of varying A-V conduction (especially if conduction varies from 2:1, 3:2; 6:3, and so on).

Variable conduction in the pathways described may also lead to variable coupling of premature systoles to the preceding beat even when it can be shown that the latter is responsible for the former. We shall demonstrate two such cases with ventricular premature systoles, in which the variations in the coupling can be explained on the basis of variations in conduction in these pathways.

**Case 1.**—Figure 1 shows the limb leads of an electrocardiogram taken on a 25 year old man with rheumatic heart disease who was not receiving medication. Numerous interpolated ventricular premature systoles are present and exhibit variable coupling with the sinus beats. The spacing between the premature systoles appears to show some constant relation when compared in the various leads. However, slight variations in the sinus rate can be observed, and with them occur similar variations in the intervals between the premature systoles (e.g., in the intervals between the last three premature systoles in strip 3 in figure 1). This fact, plus some features even better illustrated in another record (fig. 3) taken on this patient, which will be shown
below, rule out the possibility of parasystole. The unusual feature of this record is the progressive lengthening of the coupling eventually leading to the omission of a ventricular premature systole. This is strongly reminiscent of the type of progressive conduction delay seen in partial A-V block with the Wenckebach phenomenon. Thus, somewhere in one of the pathways discussed above, there is partial could have the same effect. However, this conduction delay could also occur in the pathway from the ectopic focus, or from the area of re-entry to the rest of the heart. The fact that the length of the coupling appears to be inversely proportional to the interval between the preceding two beats would seem to indicate that the conduction delay is in either of these two pathways. However, in our

Fig. 1.—Case 1. Limb leads. Strip A and B of each lead are continuous. There are numerous ventricular premature systoles with progressive lengthening of coupling, leading to the omission of a ventricular premature systole. (Discussion in text.)

block with 3:2 conduction, since every third sinus impulse is not followed by a premature systole. Can this conduction delay be in the pathway of the sinus impulse to the ectopic focus or to the region where re-entry occurs? We know from animal experiments of Scherf (see above) that changing the site of origin of the first beat may change its coupling with the premature systole that is caused by it. Then, certainly, variable conduction in such a pathway second case (figs. 4-6) the ventricular premature systoles are not interpolated, but are followed by a compensatory pause, so that this relationship does not hold. Furthermore, if either of these pathways shows variable conduction, then certainly it is not in the path of the main spread of the sinus impulse over the heart, since there is no aberrant conduction as evidenced by any changes in the contour of the sinus beat which immediately follows the premature
systole. It is therefore entirely possible that this progressive conduction delay with the Wenckebach phenomenon occurs in the re-entry pathway itself. The length of the coupling would then be related to the interval or the duration of the rest period between premature systoles. Such a relationship, present in this case, is also present in our second case.

In most Lead 1 of Case 1, every sinus beat is followed by a ventricular premature systole, i.e., 1:1 conduction in one of the pathways just discussed. However, one unusual finding is the unexpected shortening of the coupling at the end of the strip without the dropping of a ventricular premature beat. This may be due to the fact that there is simultaneous slight slowing of the sinus rate with a consequent increase in the rest period between stimuli entering the region where re-entry occurs. However, it may also be considered as the same type of phenomenon sometimes seen in partial A-V block with the Wenckebach phenomenon when occasional shortening of the P-R interval occurs without the dropping of a beat.5

Figure 2 shows the chest leads in this same case taken immediately after the limb leads, and Leads CF4 and CF5 show the development of 2:1 conduction in one of the pathways described above, since every other sinus beat is followed by an interpolated ventricular premature systole.

Figure 3 shows a portion of a very long record taken on the same patient several days later where numerous noninterpolated ventricular premature systoles are present with persistent bigeminal rhythm. The increase in sinus rate was induced by amyl nitrite inhalation. The coupling is seen to remain rather constant, increasing slightly only towards the end of the strip as the intervals between the premature systoles become shorter, and as the intervals between the two beats preceding the premature systoles also become shorter. The increase in sinus rate combined with the slight prolongation of coupling results in the inscription of fusion complexes as seen towards the end of the record, indicated by "X." Fusion beats formed in such a way are unusual. The relative consistency of the coupling in the face of such marked variation in the sinus rate rules out parasystole.

In examining long strips of the electrocardiogram in this patient it was noted that when the sinus rate was slow, every other sinus beat was followed by an interpolated ventricular premature systole. When the sinus rate became faster, bigeminal rhythm appeared, each conducted sinus impulse being followed by a noninterpolated ventricular premature systole, which was then followed by a nonconducted sinus impulse. Further increase in sinus rate leads to the disappearance of the ventricular premature systoles. All the phenomena described above could be found consistently in long strips of this patient.

The case described above is very similar to one reported by Zander25 in 1927. He suggested...
Fig. 3.—Case 1. Continuous record of Lead II. The end of each strip is reproduced again at the beginning of the strip just below it, identical beats being indicated by the same letter (A–A, B–B). Fusion complexes are marked “X.” The gradual increase in sinus rate is produced by amyl nitrite inhalation. The coupling is seen to remain rather constant, increasing slightly only towards the end of the record. (Discussion in text.)
that there existed somewhere in the conduction system of the ventricles, a small portion in which conduction was so slow that by the time the sinus impulse passed through this portion, the absolute refractory period of the ventricles variations in coupling were due not to variations in conduction but to variations in the rate of ectopic stimulus formation.

In an abstract submitted to the III Inter-American Cardiological Congress, Winternitz

was over and they could again respond. He postulated 3:2 block with the Wenckebach phenomenon in this area. This explanation, when examined closely, is one which in essence also attributes the delay to the re-entry pathway. In 1928, Goldenberg and Scherf also reported a case with similar features, but felt that the called attention to disturbances in conduction of the extrasystolic impulse in cases of auricular fibrillation which showed premature systoles with fixed coupling occurring after digitalization. In his first case, showing bigeminal rhythm, the contour of the premature systole varies with the duration of the pause preceding

Fig. 4.—Case 2. Numerous noninterpolated ventricular premature systoles are present. (The variations in coupling are discussed in text.)
the conducted beat to which the premature systole is coupled. In his second case, showing intermittent bigeminal rhythm, the occurrence of premature systoles is demonstrated to depend on the duration of the pause preceding the conducted beat to which the premature systole is coupled. These phenomena are explained by Winternitz by a partial exit block for the extrasystolic impulse in the first case and by a complete exit block in the second case.

Case 2.—Figure 4 is a record taken on a 65 year old man with arteriosclerotic heart disease, who was not receiving digitalis. Here again can be seen numerous ventricular premature systoles. Whenever two pairs of bigeminal beats follow one another, the coupling of the second pair is longer than the first. Here, however, in contradistinction to the first two records presented, the rest period preceding the pair of beats with the longer coupling appears longer than that before the pair with the shorter coupling because these premature systoles are not interpolated. It is, of course, possible that the sinus impulse which appears to be completely nonconducted may partially penetrate into an area in the ventricles near the ectopic focus, or near the area of reentry, before it is blocked and causes prolongation of the next coupling interval.27 There is, however, no definite evidence that this occurs. Another possible
explanation would be that, since the cycle length preceding the second pair of beats is longer than that preceding the first pair of beats, the conduction in one of the discussed pathways is slower. However, in figure 6 where the occurrence of a series of three and more bigeminal beats is shown, this factor will be seen not to be responsible. Thus, here again the important factor which appears to affect the coupling is the interval between the premature systoles, or in other words, the rest period in the re-entry pathway itself.

Figure 5 shows a record taken one month after the last one. The same phenomena are present.

Figure 6 shows a record taken seven months after the first one and here longer series of bigeminal beats are present in some of the leads. The shortening of the coupling towards the end of Lead III can be seen to be correlated with an increase in the interval between the premature systoles which in turn is caused by the slight slowing in sinus rate. That the progressive prolongation of coupling as seen in the last two figures was not due to the increased length of the preceding cycle can be seen also in this series of beats where the slight progressive prolongation of the cycle preceding each pair of coupled beats is nonetheless followed by shortening of the coupling. The ventricular premature systoles shown in figures 4, 5, and 6 are not due to parasystole since careful

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6.png}
\caption{Case 2. Record taken seven months after the one reproduced in figure 4. (Discussion in text.)}
\end{figure}
mensuration shows the slight variation in the inter-extrasystolic intervals to be dependent on the equally slight variations in sinus rate.

We have thus demonstrated the importance of variable conduction in one of the three pathways described above in affecting the time of appearance of premature systoles of similar contour. It should also be emphasized that a similar mechanism may operate in some cases in which the contour of the premature systoles varies. This applies to instances with fixed coupling as well as to some with progressive lengthening of the coupling. Thus, differences in contour of premature systoles, while in most instances best explained by assuming that the premature beats arise from multiple foci, may conceivably also be the result of variations in the topographic pathways selected by the impulse, as determined by variations in refractory states of adjacent regions of myocardial tissue, in its course from the single ectopic focus or area of re-entry to the rest of the heart (i.e., aberrancy of conduction). In a similar way such variations in conduction of the extrasystolic impulse may be responsible for variations in rate and in contour in some cases of paroxysmal ventricular tachycardia.

**Summary**

The purpose of this paper has been to emphasize the importance of the hidden variations in conduction in pathways usually not considered in the determination of the genesis of premature systoles.

Three possible regions may be considered where variations may occur in the conduction of the impulse which causes the premature systoles: (1) In the pathway of the impulse of the dominant rhythm to an ectopic focus, or to the region where re-entry occurs; (2) in the pathways from the point of exit from a parasystolic focus, an ectopic focus, or an area of re-entry to the rest of the heart; (3) in a region which is somewhat between the above two pathways, a region where there exists impaired conduction making the phenomenon of re-entry possible, namely, the re-entry pathway itself.

The mechanism which in any given case may be responsible for premature systoles (parasystole, re-entry, and impulse formation by an ectopic focus) is discussed. It was suggested that variations in conduction in one or more of the above pathways could affect significantly the time of appearance of premature systoles owing to any of the above mechanisms. Thus, fixed coupling could not be considered a condition sine qua non for the diagnosis of a re-entry mechanism, and, similarly, parasystole cannot always be ruled out because of variations in the inter-extrasystolic intervals.

It was suggested that similar factors may be present in some cases in which the premature systoles have a variable contour, and in some cases of paroxysmal ventricular tachycardia with varying rate and complexes of varying contour.

It was demonstrated that while it may often be impossible to determine its exact site, the existence, at least, of such varying conduction could often be detected as in two cases with numerous ventricular premature systoles which were presented.

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