XI. Coupling Intervals of Ventricular Extrasystoles in Relation to the Heart Rate, the U Wave, and the Supernormal Phase of Excitability

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According to our present state of knowledge it seems very probable that the U wave of the electrocardiogram is caused by the summation of afterpotentials in cardiac muscle, and that the normal positive U waves are caused by the summation of negative afterpotentials. Since these potentials are accompanied in nerve or muscle by a temporary reduction of the threshold of excitability (supernormal phase of excitability), it follows that the U wave must correspond to this supernormal phase, as was first suggested by Nahum and Hoff, who observed that coupled ventricular extrasystoles usually occur during the writing of the U wave. In the present paper it was intended to test this concept by determining whether or not factors that alter the amplitude or time of appearance of the U wave have a corresponding effect on the incidence or time of appearance of ventricular extrasystoles. Furthermore, it was of interest to know whether persons showing primary U-wave inversion, which was attributed to the appearance of positive afterpotentials corresponding to a phase of subnormal excitability, show a different incidence or timing of extrasystoles than persons with normal U waves.

One of the most important factors that influence the time of appearance of the U wave is the heart rate. Therefore it was important to determine whether in the regularly beating heart the coupling interval of ventricular extrasystoles decreases with increasing heart rate in the same way as does the duration of the Q-U interval. In figure 11 of Nahum and Hoff's paper it can be seen that, in 10 patients showing an R-R interval of 0.50 sec. and an average Q-T interval of 0.36 sec., the coupling interval of extrasystoles (Q-E interval) ranged between 0.29 and 0.42 sec.; in 67 patients with R-R intervals of 0.60 to 0.80 sec. and an average Q-T of 0.30 to 0.40 sec., the Q-E interval ranged between 0.40 and 0.65 sec.; while in 11 cases with an R-R interval about 1.00 sec. and an average Q-T interval of 0.36 sec. the Q-E intervals ranged between 0.65 and 1.00 sec. Only the extrasystoles of the second group were said to appear during the U wave, whereas those of the first group appeared while the descending branch of T was being written and those of the third group appeared during and after the inscription of the P wave. Koulu-mies and co-workers stated that of 500 cases with prominent U waves extrasystoles were present in 27, appearing during the U wave in 25 and during the P wave in 2 cases. Zuckermann and Estandia stated that in 300 instances mechanical stimulation of the septal region of the ventricle in dogs always caused extrasystoles, which appeared late (during or after the P wave), while stimulation of the free walls of the ventricle led to extrasystoles appearing during or immediately after the inscription of the T wave, where a U wave would have been found, if it were present in dogs. In their figure 7 the authors showed that in human subjects about 70 ventricular extrasystoles appeared synchronously with the U wave, while 7 appeared after it and during the P wave or P-R segment. These latter extrasystoles, which the authors considered to originate in the ventricular septum in analogy to the findings in dogs, were characterized by an initial slurring of the QRS, which was upright in the left as well as the right precordial

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leads. The initial slurring was also present in the septal extrasystoles produced experimentally in dogs.

In order to study the coupling intervals of ventricular extrasystoles in relation to their configuration as well as to the heart rate, the coupling intervals (Q-E) of 250 personal cases, in which at least 3 ventricular extrasystoles were registered, were plotted in figure 1 in relation to the average R-R interval of each case. Since the number of cases showing extrasystoles at ventricular rates exceeding 100 was too small to warrant any definite conclusions, 10 additional measurements were made on electrocardiograms of such cases published in the paper of Berliner and Huppert. Each case is represented by an oval that contains all the measured Q-E intervals. In addition to these 250 cases, very long tracings, containing at least 20 extrasystoles, were taken in 20 cases in a single lead; these correspond to the very long ovals in figure 1. If the coupling intervals fell into 2 or more distinct groups, these groups are indicated by ovals connected by continuous vertical lines. If the coupling intervals were studied at 2 different heart rates in the same case, the ovals corresponding to these intervals are connected by continuous diagonal lines. The average Q-T and Q-aU intervals for each heart rate are indicated by dashed or dotted curves respectively. If in a given case these intervals are significantly different from the average, they are indicated by a dash or dot, respectively, connected to the corresponding Q-E interval by an interrupted vertical line. The diagonal straight line at the upper left hand corner indicates the natural limit of Q-E for each Q-Q interval, that is, the value of Q-E at which it is equal to Q-Q. Extrasystoles that

Fig. 1. Relation of the coupling intervals of ventricular extrasystoles (Q-E, on ordinate) to the preceding pulse interval (Q-Q, on abscissa), in 250 cases (represented by circles and ovals). Dotted curve, average Q-aU intervals; dashed curve, average Q-T interval for each pulse interval. All values are in hundredths of a second.
have a coupling interval exceeding this value will not appear at all at a given heart rate.

An attempt was made to estimate the speed of the initial component of ventricular extrasystoles by determining the maximum voltage developed in any lead during the first 0.04 sec. of the QRS complex; if this voltage did not exceed 2 mm., the beginning of the extrasystole was said to be slow; the ovals corresponding to such extrasystoles in figure 1 were shaded. Extrasystoles appearing in persons showing primary (isolated) inversion of the U wave were designated by the letter "U" next to the corresponding ovals. Extrasystoles appearing in persons treated with digitalis and showing a configuration of T and S-T typical for the digitalis effect were marked with the letter D, those appearing under the influence of epinephrine were marked with the letter E, and those appearing in hypopotassemia were marked with the letter H next to the corresponding ovals.

Figure 1 shows first of all that the average value of the coupling intervals increased with falling heart rate, and that this increase approximately paralleled that of the Q-aU interval; the great majority of the single values seem to be situated between Q-T and a curve about 0.5 sec. above the Q-aU curve. In all cases where the same type of ventricular extrasystoles appeared at widely different heart rates (circles connected by diagonal lines) the coupling intervals were shorter at the higher rate (fig. 1). In 5 cases in which extrasystoles appeared in groups of 2 or more, the coupling interval was always shorter in the second extrasystole, corresponding to the shorter pause preceding the beat to which the extrasystole was coupled; this is a common finding. In such cases it seemed that the extrasystoles originated at the same point on the U waves regardless of their coupling intervals.

In the 20 cases in which a very large number of extrasystoles was registered in the same lead, when the extrasystoles appeared in bigeminal rhythm or regularly after every 2 or 3 normal beats, the coupling intervals remained constant within 0.02 sec. However, when the extrasystoles occurred irregularly, the coupling intervals varied on the average 0.04 sec. and in some cases up to 0.11 sec. In all these cases the extrasystolic beats were truly coupled to the preceding normal beats, for they did not appear in the latter half of the diastolic period. In 4 cases, however, 2 groups of coupling intervals were found; the intervals

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**Fig. 2.** A. Lead V5, with the heart sounds superimposed upon it in the second half, in a 68-year-old woman with severe vomiting and diarrhea. The tall late upright waves that appear as diphasic T waves are in reality tall U waves, since their apex appears very late, long after the second heart sound (indicated by arrows). B. Lead II in the same case. The serum potassium at this time was 2.5 mEq./L., the serum sodium 110 mEq./L. C. Lead II after infusion of potassium in dextrose solution (the amount of potassium evidently was not sufficient to counteract the potassium fixation caused by dextrose). The U waves are now taller than the R waves. D. The U waves are even taller, and ventricular extrasystoles appear at their summits. E. The ventricular extrasystoles are followed by short runs of ventricular tachycardia. The infusion was discontinued at this point. F. Ventricular flutter. G. Ventricular fibrillation. These electrocardiograms were registered by D. Lareau, M.D. and interpreted by B. Surawicz, M.D.
within each group did not vary more than 0.11 sec., and in all cases the configuration of the extrasystoles in these 2 groups was different. In all these cases with slightly variable coupling intervals measurement of the interextrasystolic intervals showed that a parasystolic rhythm could be held responsible for them only under the assumption that the rate of this rhythm varied more than 10 per cent. The maximal variation of the coupling intervals in a given case therefore exceeds the 0.04 quoted by Scherf and Schott.4

In 34 cases (about 13 per cent of the series) the extrasystoles appeared very late in diastole, long after the apex of the U wave; these extrasystoles seemed to be distributed evenly throughout the diastole without relation to the heart rate. In 28 of these (fig. 3) the extrasystoles began with a slow initial component, while of the 185 remaining cases in which the
slopes of the initial component were determined, only 65 showed a slow slope. In all 4 cases that showed both the late and the early type of extrasystoles, the former always had a slow initial component while in the latter this component was rapid. In figure 127 of Scherf and Schott, where the coupling intervals were unusually long (1.12 sec.), the initial slope was also relatively slow. Thus the observations of Zuckermann, mentioned in the introduction, were confirmed in general. However, in the 35 cases where extrasystoles were registered in all precordial leads, there was no apparent relation between the coupling intervals and the direction of QRS in these leads.

In the cases where ventricular extrasystoles appeared after digitalis (D) or in hypopotassemia (H) the coupling intervals did not differ appreciably from the usual values at the same heart rate, although in the case of digitalis Q-T was definitely shorter; in both groups the apex of U appeared at the usual time. However, in extrasystoles appearing during administration of epinephrine (E) the coupling intervals were usually either considerably outside of the usual range for the heart rate, or on the lower limit of this range; in 2 cases it could be seen that the average coupling intervals decreased parallel to a decrease in the Q-U interval while Q-T retained its normal relation to the heart rate (fig. 4). As for extrasystoles in the presence of isolated inverted or diphasic U waves, these could be observed in only 4 cases. In all of these the coupling intervals were on the upper border of the usual values for the heart rate; in 1 case (fig. 2) these intervals became average in the upright position, when the heart rate increased and the U wave became completely positive.

In 7 cases the coupling of ventricular extrasystoles was shorter than the average Q-T interval; in all these cases the extrasystoles began before the end of the T wave. Four of these had fresh myocardial infarction while 3 had advanced cardiac failure incident to hypertensive heart disease (fig. 1); 2 of the latter group were receiving digitalis but did not show the typical digitalis pattern in the electrocardiogram. In all 7 cases the extrasystoles had a rapid initial component; in 3 there were other ventricular extrasystoles of a different configuration that showed coupling intervals of an average duration.

**Discussion**

There are 2 groups of explanations for coupled extrasystoles. According to the re-entry hypothesis, some section of the conducting system may have a prolonged refractory period and accordingly not be excited when first reached by the normal impulse; when the same impulse reaches it shortly afterwards by another pathway, it then excites the region, since its refractory period would be over. Owing to slow velocity of conduction within it, this region would not re-excite the rest of the ventricle until after a period corresponding to the coupling interval of the extrasystoles. According to this explanation, the extrasystole would occur only if the normal beat happens to occur exactly at the end of the prolonged refractory period; appearance of coupled extrasystoles at widely varying heart rates in the same person would not be explained by it. Furthermore, according to any hypothesis that attributes the coupling interval to a greatly prolonged focal conduction, this interval would be expected to show a marked increase with rising heart rate; actually this interval in general decreases with rising rate (fig. 1). The re-entry hypothesis has not been proved, and numerous objections have been advanced against it.

An explanation which has been proved to apply even to single cells by means of intracellular electrodes is that coupled extrasystoles are caused by a temporary increase in excitability following the relative refractory phase (supernormal phase of excitability). Theoretically, there are 2 possibilities for the appearance of extrasystoles due to the supernormal phase. In the first, a constant stimulus (a constant slight depolarization of the cell membrane) is present in some circumscribed region of the myocardium. If this stimulus is very weak, it will excite only at the peak of the supernormal phase of excitability; if it is stronger it will excite earlier, at the beginning of this phase. Finally, if the stimulus is very strong, it will excite at the end of the absolute refractory phase, and the coupling intervals will be extremely short, the extrasystoles ap-
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pearing very soon after the apex of the T wave. In any case the coupling intervals should be constant.

The second possibility is that the stimulus is not constant but arises in a parasystolic center that is so weak that it can excite the muscle surrounding it only during the supernormal phase. This possibility was mentioned by Schaefer. In this case, if the rhythmic stimulus is weak, it will cause extrasystoles only occasionally, when it occurs at the height of the supernormal phase, and the coupling intervals will be approximately the same. If the stimulus is stronger it will excite also at the beginning and at the end of the supernormal phase; the extrasystoles will be more abundant and their coupling intervals will vary within the limits of 0.10 to 0.25 sec. (which is the duration of the supernormal phase).

In both possibilities discussed above the duration of the coupling intervals is complicated by the fact that there may be a considerable conduction delay ("perifocal block") between the site of origin of the extrasystoles and the neighboring myocardium. The magnitude of this delay may depend on the pause between the regular heart beats if this perifocal tissue is excited also by the normal beats, or it may depend on the pause between extrasystoles if it shows protective block from the normal beats and is excited only by the extrasystoles. We can, therefore, reach the conclusion that, while in general the coupling of extrasystoles decreases with rising heart rate due to earlier occurrence of the supernormal phase, a perifocal conduction delay may counteract or even reverse this tendency in a given case. The great variability of the coupling intervals found in some of our cases (long ovals in fig. 1) can be attributed to this factor, while in others it could have been due to a parasystolic nature of the stimulus.

The supernormal phase of excitability in the frog heart was found to correspond to the negative afterpotentials, and was attributed, as in nerve, to partial depolarization of the cell membrane by these afterpotentials. This depolarization reduces the strength of stimulus needed to reduce the membrane potential to critical levels, at which the sodium permeability exceeds the potassium permeability, initiating a spontaneous action potential. If the normal U wave is caused by negative afterpotentials, then a supernormal phase should be present whenever definite U waves can be seen. Actually, a supernormal phase was found in all cats and monkeys under barbiturate anesthesia with natural respiration but only occasionally or not at all in cats and dogs under artificial respiration. In studies with greater precision of measurement a supernormal phase was frequent, but it corresponded to a decrease of threshold of only 5 to 15 per cent. The reason for this difference may be that the depressed respiration due to barbiturates and a partly opened chest probably leads to acidosis, while artificial respiration tends to produce hyperventilation and alkalosis; the supernormal phase was found to be especially marked in an acid reaction or in "fatigued" hearts or excised myocardial strips, where hypoxia and acidosis are probable. The only occasional occurrence of the supernormal phase in the normal dog heart is not in conflict with the concept concerning the genesis of the U wave mentioned above, since dogs normally show no recognizable U waves. Studies on the cardiac excitability in man or in other animals having tall U waves have not been carried out. On the other hand, the absence of a U wave does not preclude the appearance of extrasystoles due to a supernormal phase, since negative afterpotentials could be present in the very small localized region of the myocardium that gives rise to extrasystoles, without appearing in the surface electrocardiogram. A local increase in acidity favoring the appearance of a supernormal phase can very well be the result of focal coronary sclerosis or myocarditis, which is responsible for extrasystoles in most cases. The fact that the coupling intervals of ventricular extrasystoles were influenced by epinephrine, digitalis, and especially by changes in the heart rate in approximately the same way as the Q-aU interval, is in keeping with the assumption that these extrasystoles are caused by the supernormal phase of excitability.

The great majority of ventricular extrasystoles studied by us began during the period extending from 0.03 sec. after the end of the T wave or the beginning of the U wave to about
0.05 sec. after the apex of the U wave. If the beginning of the U wave corresponds to the plateau of the negative afterpotential while the apex of the U wave corresponds to its descending branch, this observation would indicate that the extrasystoles begin during the ascending branch or the apex of the supernormal phase of excitability, if a perifocal conduction interval of 0.01 to 0.05 sec. is assumed. The extrasystoles with fairly constant coupling intervals can then be interpreted as being elicited by a constant stimulus while those with variable coupling intervals might be caused by a parasystolic stimulus. That no common denominator could be found for the interextrasystolic intervals in our cases would not exclude a parasystolic stimulus, since the rate of such a stimulus, as well as the perifocal conduction time, can vary considerably.

It was mentioned that cases with isolated diphasic (±) U waves showed coupling intervals exceeding the average intervals found at the particular heart rate in the few cases studied. If this observation should be confirmed on a larger series, it would definitely be in favor of this form of U waves being due to the appearance of diphasic (−+) afterpotentials, since then the supernormal phase, which would correspond to the negative phase of such afterpotentials, would be expected to begin late.

In the light of our concept concerning the genesis of the U waves, we would expect that all factors that increase the amplitude of the U waves would also facilitate the appearance of coupled extrasystoles. In the amphibian heart, there seems to be an exact parallelism between the amplitude of the negative afterpotential, the supernormal phase, and the appearance of these extrasystoles. In the mammalian heart, this same parallelism is present following the administration of epinephrine, calcium, and digitalis; the prevalent type of extrasystoles elicited by these drugs is the coupled one, with the ectopic beat beginning at the peak of the elevated U waves. In hypopotassemia, where elevation of U waves is one of the most constant signs, ectopic beats are common, but usually are of supraventricular origin. However, when they do originate in the ventricles, they always appear at the summit of the U waves. Figure 3 shows the development of coupled ventricular extrasystoles parallel to increase in the amplitude of the U wave in a case of hypopotassemia; during the U wave of these extrasystoles other extrasystoles appeared, and this evidently led to re-entry and ventricular flutter and fibrillation. The same sequence was observed recently in rabbit hearts perfused with a low potassium solution. On the other hand, potassium decreases the U waves and the afterpotentials, and suppresses all coupled extrasystoles.

In acidosis, which is known to elevate the U waves, a supernormal phase was found to appear in the mammalian heart, and this was accompanied by the appearance of ventricular extrasystoles with coupling intervals corresponding to the duration of this phase. Slowing of the heart rate, which tends to elevate the U waves, also favors the appearance of coupled rhythms; we have seen this event in many cases of atrial fibrillation treated with digitalis, where coupled extrasystoles were precipitated only by ventricular complexes appearing after long pauses. This observation was made previously.

The only discrepancy between the amplitude of the U waves and the effect on excitability is the suppression of coupled extrasystoles by quinidine in spite of its elevating effect on the U waves; the explanation of this peculiarity could be that the threshold of excitability is raised to such a degree by quinidine that even the presence of an increased supernormal phase still does not lower it sufficiently for excitation by the ectopic stimulus.

The few extrasystoles with very short coupling intervals found in figure 1 could be explained by the presence of a very intense continuous stimulus, which excites at the end of the absolute refractory phase and before the end of the T wave. In the case of acute myocardial infarction or congestive heart failure, localized partial depolarization of the muscle membrane can act as such a stimulus. All patients exhibiting such short coupling intervals were in grave condition. This association was also found by Smirk, although in some of his cases R waves of extrasystoles
interrupted T waves not because the coupling intervals were short, but because the Q-T intervals were prolonged.

In the extrasystoles that appeared after the U wave and therefore showed long coupling intervals in figure 1, a relation between these intervals and the heart rate was present only inasmuch as these extrasystoles could not appear at fast heart rates, when the Q-Q interval was shorter than the coupling interval; beyond this minimal Q-Q interval there seems to be no relation to the heart rate. The best explanation for these extrasystoles is that they are caused by automatic stimulus formation, that is, that they represent escape beats with a short preautomatic pause. Such automatic stimulus formation is the result of gradual membrane depolarization during diastole, culminating in a prepotential of rapidly increasing amplitude; when this prepotential reaches the critical membrane potential, the membrane is depolarized and a conducted action potential results.6 7 The fact that nearly all extrasystoles appearing late in diastole began with a slow initial component gives support to this interpretation.

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