Characterization of oscillations in ventricular refractoriness in man after an abrupt increment in heart rate

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ABSTRACT  Oscillations in ventricular myocardial refractoriness after a change in rate have not been described in man. During 25 baseline paced cycle lengths ($S^0-S^0$) of 400 to 800 msec in 14 patients, a shorter cycle length ($S'-S'$) was introduced that was 10 to 20 msec (mean 15 ± 5) greater in duration than the ventricular effective refractory period (VERP) determined after 12 beats of the respective baseline cycle length (group 1 trials). In addition, during 14 of the 25 baseline cycle lengths, a second shorter cycle length was introduced that was 50 to 80 msec (mean 65 ± 10) greater than the VERP of the respective baseline cycle length (group 2 trials). In all 39 group 1 and group 2 trials the VERP was determined after each of at least 3 beats ($S'_1, S'_2, S'_3$) of the shorter cycle length and in six of the 25 group 1 trials the VERP was determined after each of at least 12 beats of the shorter cycle length. In all group 1 trials oscillations of the VERP were observed, with a mean $S'_1$ VERP of 202 ± 28 msec, an $S'_2$ VERP of 228 ± 25 msec ($p < .001$ vs $S'_1$ VERP), and an $S'_3$ VERP of 210 ± 26 msec ($p < .001$ vs $S'_2$ VERP). Oscillations dampened within 4 beats, but persisted at a lower amplitude in four of the six group 1 trials during which the shorter cycle length was maintained for at least 12 beats. In group 2 trials, oscillations in VERP were never seen with an $S'_1$ VERP of 238 ± 27 msec, an $S'_2$ VERP of 233 ± 25 msec ($p < .01$ vs $S'_1$ VERP) and an $S'_3$ VERP of 232 ± 27 msec ($p = NS$ vs $S'_1$ VERP). In six of the patients a series of shorter cycle lengths ranging from 10 to 100 msec greater than the VERP of the baseline length were introduced and in all cases the amplitude of the initial oscillation in VERP was noted to be inversely related to the increment by which the new cycle length exceeded the VERP of the baseline cycle length. In summary, oscillations in VERP in man (1) occur after an abrupt change to a shorter cycle length that approaches the VERP of the baseline cycle length, (2) rapidly dampen but may persist at a low amplitude when the shorter cycle length is maintained, and (3) have an initial amplitude that is inversely related to the increment by which the new cycle length exceeds the VERP of the baseline cycle length. These oscillations in VERP may contribute to arrhythmia initiation and termination.


THE EFFECTS of both drive cycle length and prematurity of a single extrastimulus on ventricular myocardial refractoriness in man have been extensively characterized.1–4 Furthermore, the time course of changes in ventricular myocardial refractoriness in man after a persistent change in paced cycle length has also been described.5 Although Tchou et al.6 have described oscillations in His-Purkinje refractoriness, oscillations in ventricular myocardial refractoriness after a change in rate have not been previously observed in man. The failure of Tchou et al. to observe these oscillations may have been related to the relatively long cycle lengths used in characterization of the changes in ventricular myocardial refractoriness after an abrupt increase in heart rate. These oscillations in ventricular myocardial refractoriness may have important implications for ventricular tachyarrhythmia genesis and termination. This study was designed (1) to determine whether oscillations in ventricular myocardial refractoriness occur in man after a marked shortening of the cycle length, (2) to define the characteristics of oscillations...

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during a maintained shortening of the cycle length, and (3) to determine whether the presence and amplitude of oscillations in ventricular myocardial refractoriness are critically dependent on the increment by which the new cycle length exceeds the refractoriness of the baseline cycle length.

Methods

Patient population. There were 11 men and three women in the study population who ranged in age from 25 to 62 years. Seven of the patients had no structural heart disease, two patients had coronary artery disease, two patients had dilated cardiomyopathy, one patient had hypertrophic cardiomyopathy, and one patient each had valvular and hypertensive heart disease. All patients were undergoing electrophysiologic study for evaluation of documented supraventricular (two patients) or ventricular (two patients) arrhythmias or suspected arrhythmias (10 patients with presyncope or syncope in the absence of electrocardiographic documentation of the rhythm at the time of symptoms). The stimulation protocol used in this study was begun after completion of the routine evaluation of documented or suspected arrhythmias by previously described techniques. Three of the 14 patients were being treated with antiarrhythmic medications at the time of study. Antiarrhythmic medications included disopyramide, procainamide, and quinidine with propranolol in one patient each.

Stimulation protocol. During 25 baseline paced cycle lengths ($S^B-S^B$) ranging from 400 to 800 msec (table 1), the ventricular effective refractory period (VERP) was determined after each of 12 beats of the baseline cycle length with the use of extrastimulus initially introduced late in diastole. The coupling interval of the extrastimulus was then decreased by 2 to 5 msec until a ventricular response was no longer evoked. Each 12 beat drive train and extrastimulus was followed by a 5 sec pacing pause during which sinus rhythm was reestablished. In each of the 14 patients the baseline cycle length equalled the longest cycle length that permitted uninterrupted capture. In five of the 14 patients, one to three additional shorter paced cycle lengths were also used as the baseline cycle lengths (table 1). The additional baseline cycle lengths differed by at least 100 msec. Each 12 beat drive and extrastimulus was followed by a 5 sec pacing pause. The VERP was defined as the longest coupling interval of the extrastimulus that failed to evoke a ventricular response. All stimulation was bipolar (0.5 cm interelectrode distance). Stimulation was performed at the right ventricular apex with a current strength that was two times diastolic threshold with a 1 msec pulse width.

After the VERP was determined for the baseline drive cycle length, a shorter cycle length (figure 1) was introduced from the same right ventricular apical pacing site. The shorter paced cycle length was introduced after 12 beats of the baseline cycle length ($[S^B-S^B = S^B-S^B]$) and the VERP was determined after each beat ($S^B$) of up to 19 beats (see below) of the shorter cycle length with use of an extrastimulus ($S_{n,n+1}$) decreased by 2 to 5 msec intervals. The baseline cycle length was always reestablished for 12 beats after the extrastimulus and a 5 sec pacing pause. The first coupling interval of the extrastimulus was at least 20 msec greater than the VERP of the previous beat and always resulted in ventricular capture before its coupling interval was decreased.

Study protocol. The described stimulation protocol was used in all three parts of the study. The first part of the study protocol was designed to determine whether oscillations in ventricular myocardial refractoriness exist after a sudden marked shortening of the cycle length. A shorter cycle length was introduced during 25 baseline cycle lengths, with the shorter cycle length exceeding the VERP of the respective baseline cycle length by only 10 to 20 msec. There were designated group 1 trials ($n = 25$). During 14 of the initial 25 baseline cycle lengths (table 1), a second shorter cycle length was subsequently introduced that exceeded the VERP of the baseline cycle length by 50 to 80 msec. These were designated group 2 trials ($n = 14$). The VERP was determined after each of 3 beats ($S_1', S_2', S_3'$) of the new shorter cycle length in all 39 group I and group II trials.

The second part of the study protocol attempted to define the characteristics of the oscillations with a persistent shortening of the cycle length. In six of the 25 group 1 trials ($S^B-S^B = 500$ msec in three trials and 400 msec in three trials), the VERP was determined not only after the first 3 beats but also each of at least 12 beats ($S_1', . . . , S_{12}'$) of the shorter cycle length (range 12 to 19 beats). The persistent pacing at the shorter cycle length was only performed in patients without structural heart disease. No sustained arrhythmias were initiated as a result of stimulation.

The third part of the study protocol was designed to define further the relationship between the increment by which the new shorter cycle length exceeded the VERP of the baseline cycle length and the presence and amplitude of oscillations in ventricular refractoriness. To achieve this goal the following protocol was used during six baseline drive cycle lengths: (1) The VERP was determined after each of three beats ($S_1', S_2', S_3'$) of the shorter paced cycle length, with the shorter cycle length 10 to 20 msec greater than the VERP of $S^B$. (2) The new cycle length ($S_{-}^B - S_{-}^B$) was then increased in 20 msec increments and the VERP was determined after each of the first 3 beats of the incremented cycle length. This process was repeated until the new cycle length was 70 to 100 msec greater than the VERP of $S^B$, and oscillations in refractoriness were no longer observed.

Statistical analysis. The VERP of each of the first 3 beats ($S_1', S_2', S_3'$) of the new shorter cycle length was compared with the VERP of the preceding beat of the new shorter cycle length except in the case of $S_1'$. The VERP of this $S_1'$ was compared with the VERP determined after 12 beats of the baseline drive cycle length. Student's $t$ test for paired data was used to compare VERPs. A $p < .05$ was considered indicative of a statistically significant difference.

Results

In each of the group 1 trials, regardless of the value of the baseline cycle length (400 to 800 msec) or the presence of structural heart disease in the patients studied, oscillations in VERP were observed, while in each of the group 2 trials, a shortening or no change in VERP was observed after each beat of the newly introduced cycle length (summary data are shown in figure 2). In group 1 trials the new shorter cycle length was 15
± 5 msec greater in duration than the VERP determined after 12 beats of the respective baseline cycle length. In group 2 trials the new cycle length was 65 ± 10 msec greater than the VERP determined after 12 beats of the respective baseline cycle length. In all group 1 and group 2 trials, the VERP of S'1 decreased compared with the VERP determined after 12 beats of the baseline cycle length. In group 1 trials, the VERP of S'1 increased by a mean of 19 ± 10 msec (range 5 to 50) compared with the VERP of S'1 (p < .001). This increase in VERP of the second beat of the new drive was followed by a decrease in the VERP of S'1 by 12 ± 5 msec (range 5 to 20); p < .001 compared with VERP of S'1. In contrast, in group 2 trials the VERP of S'1 was 5 ± 3 msec (range 0 to 10) less than the VERP of S'1 (p < .01), and the VERP of S'1 was 1 ± 3 msec (range 0 to 5) less than the VERP of S'1 (p = NS).

Effect of a persistent shortening in cycle length. Oscillations in VERP with a change to a cycle length 10 to 20 msec greater than the VERP of the baseline cycle length were observed to dampen after 4 beats (figure 3). When a maintained shorter cycle length was introduced during baseline cycle lengths of 500 or 400 msec, two patterns were observed. In the first pattern, dampened oscillations (≤10 msec) in VERP persisted for at least 12 to 19 beats of the new cycle length. This pattern was observed in four group 1 trials. In each of these trials, the new cycle length was just 10 msec above the VERP of the baseline drive cycle length. In the second pattern, after initial oscillations rapidly dampened, a progressive decrease in VERP with additional beats of the new drive cycle length was noted. This pattern was observed in the remaining two group 1 trials. In both of the group 1 trials that showed the second pattern, the new cycle length was 20 msec greater than the VERP of the baseline cycle length and at least 60 msec greater than the VERP of S'1.

Effects of the relationship of S'-S' and VERP of S' on presence and amplitude of oscillation. Both the presence...
and amplitude of the initial oscillation in ventricular myocardial refractoriness were critically dependent on the value of the new cycle length relative to the VERP of the baseline cycle length (figure 4). The amplitude of the initial oscillation in VERP was maximal when the value of the new cycle length was just above (10 to 20 msec) the VERP of the baseline cycle length. The amplitude of this initial oscillation decreased when the new cycle length increased. Oscillations were never observed once the $S'$-$S'$ was greater than 50 msec above the VERP of the baseline cycle length.

**Discussion**

This study demonstrates that oscillations in ventricular myocardial refractoriness occur after a sudden change to a shorter cycle length in man. The development of these oscillations does not appear to be dependent on the value of the baseline cycle length, when it is between 400 and 800 msec, or the presence of structural heart disease or antiarrhythmic therapy. These oscillations, however, appear to occur only when the interval of the $S'$-$S'$ approximates the value of the VERP of the $S^a$-$S^b$. In fact, oscillations of 5 msec or more are not observed when the new cycle length is more than 50 msec greater than the VERP of the baseline cycle length. Of note, the amplitude of the initial oscillation in refractoriness is inversely related to the increment by which the new cycle length exceeds the VERP of the baseline cycle length. Furthermore, these oscillations in VERP diminish rapidly with additional beats at the shorter cycle length. Small amplitude (less than 10 msec) oscillations may, however, persist when the new cycle length approximates the VERP of the baseline drive cycle lengths of 400 and 500 msec.

Jansen et al. previously described oscillations in the refractoriness of ventricular myocardium after sudden changes in rate in the canine heart. Unlike the present study, the oscillations in refractoriness did not begin until the third beat ($S'_3$) of the new cycle length. A progressive decrease in the VERP of the first ($S'_1$) and second ($S'_2$) beats of the shorter cycle length was consistently observed. Of note, in the present study, an increase in the VERP of the third beat ($S'_3$) of the new cycle length was never observed. The basis for the difference in the response is unknown; however, it is premature to attribute the discrepancy solely to species differences or differences in conditions of study, i.e., unsedated man vs anesthetized dogs in whom atrioventricular block had been created by electrocautery. The stimulation protocol used by Jansen et al. differed in three ways from that of the present study: (1) in their study, a new cycle length (always 300 msec) was only introduced after a prolonged period of pacing (up to 500 beats) at the baseline cycle length (always 600 msec), (2) the new cycle length was always 30 to 90 msec greater than the VERP of the baseline cycle length, and (3) 1 msec decrements in the extrastimulus coupling interval were used to assess refractoriness.
after the rate change. The more prolonged period of pacing would have the effect of shortening the VERP of the baseline cycle length, thus resulting in a less marked shortening in the VERP after the first beat of the new cycle length. In addition, as demonstrated in the present study, the introduction of a new cycle length 30 to 90 msec greater than the VERP of the baseline cycle length is more likely to result in a progressive decrease in VERP of S'\textsubscript{1} and VERP of S'\textsubscript{2}. Finally, a 1 msec decrement in the coupling interval of the stimulus might allow for the recognition of smaller changes between the VERP of each subsequent beat of the new cycle length than is possible with the use of 2 to 5 msec decrements, thus permitting Janse et al.\textsuperscript{9} to recognize small oscillations beginning with the VERP of S'\textsubscript{3}, even when the new cycle length exceeded the VERP of the baseline cycle length by more than 50 msec.

Other investigators have demonstrated oscillations in action potential duration after a sudden increase in stimulation frequency in animal ventricular muscle preparations.\textsuperscript{10-15} The shortest action potential duration was observed for the first impulse at the faster rate. The second action potential duration was slightly longer than the first. These changes in action potential duration are consistent with the observed changes in VERP in man demonstrated in the present study. Hauswirth et al.\textsuperscript{15} attributed the oscillations in action potential duration to variations in the decay of the time- and voltage-dependent \textit{i}_s current carried by potassium. Others have attributed the changes to variations in the inactivation of the calcium-dependent slow inward current.\textsuperscript{11} According to both explanations, membrane recovery that begins on completion of the action potential is incomplete when the stimulus is introduced at an interval just longer than the effective refractory period, i.e., before the end of the action potential of the baseline cycle length. This results in a marked shortening of the action potential duration associated with the first stimulus at the faster rate and a longer period of membrane recovery before the next stimulus is introduced at the same coupling interval. The longer period of membrane recovery results in a longer action potential duration associated with the second stimulus.
brane recovery is again incomplete when the third stimulus is introduced at the same coupling interval, and a shorter action potential results. This alternation of action potential duration thus results from a shifting to and fro of the electrical restitution curve.  

The electrical restitution curve as described by Boyett and Jewell\(^{11}\) is an exponential function that relates the coupling interval of a given test stimulus to its action potential duration. The curves were generated by introducing a test stimulus during steady-state baseline pacing or after a given beat of a new shorter cycle length. The coupling interval of the test stimulus that results in a plateau value for the action potential duration is considered to reflect primarily the time course with which membrane conductances return to their prestimulus values. The test stimulus with the closest possible coupling interval, limited only by the absolute refractory period, will thus be introduced well before membrane conductances have returned to baseline and will be associated with the most marked shortening of action potential duration. When the pacing rate is abruptly increased there is a continuous shift in the point on the electrical restitution curve at which the subsequent beat of the new shorter cycle length occurs. This results in an alternation of action potential duration with added beats of the new shorter cycle length.

With a maintained increase in rate there is a shift of the electrical restitution curve both to the left and downward. This shift has been attributed to the accumulation of calcium intracellularly, which in turn may alter the time-dependent potassium current, \(i_{K}\), favoring early membrane repolarization.  

The shift of the electrical restitution curve to the left results in a gradual dampening in the oscillations of action potential duration as each subsequent stimulus introduced at the same coupling interval begins to fall closer to the plateau of the curve. The gradual downward shift of the electrical restitution curve is associated with a gradual decrease in action potential duration until a steady-state value is reached after a prolonged period of maintained pacing at the shorter cycle length.

This description of the changes in action potential duration that occur with abrupt increases in rate in ventricular muscle preparations may help to explain why the initial oscillation in VERP observed in man is of greatest amplitude when the first beat of the new shorter cycle length is introduced at an interval just above the VERP of the baseline cycle length; i.e., it is associated with the maximum difference in the period of membrane recovery between beats. It also helps to explain the basis for the rapid dampening of oscillations in VERP after 3 beats of the shorter cycle length and explains why dampened oscillations were followed by a gradual decrease in VERP in two of the six group I trials during which the VERP was measured after each of at least 12 beats of the faster cycle length. Of note, Spear and Moore\(^{16}\) demonstrated that oscillations in action potential duration, even under steady-state conditions, may persist at very rapid stimulation rates. Boyett and Jewell,\(^{11}\) have attributed the persistent oscillations in action potential duration to the fact that membrane recovery is never complete at very fast rates and that each new stimulus falls on the ascending portion of the electrical restitution curve, thus preventing the self-canceling mechanism and resolution of oscillations. During the present study, oscillations in VERP persisted for the 12 to 19 beats after a change to a shorter cycle length in four of six group I trials during which the VERP was measured after each of at least 12 beats of the shorter cycle length. These persistent oscillations were only observed after a change to a cycle length that was 10 msec above the VERP of the baseline drive cycle length. The baseline drive cycle length during this part of the present study was always 400 or 500 msec. It is reasonable to assume that these new rates were sufficiently fast to prevent complete membrane recovery and created persistent oscillations in action potential duration and ventricular refractoriness.

The present study initially appears to conflict with work recently reported by Tchou et al.\(^{5}\) These investigators noted the presence of oscillations in His-Purkinje but not ventricular myocardial refractoriness in man after abrupt accelerations in heart rate. They noted that the mode of adaption in refractoriness of the His-Purkinje system in man after a sudden rate accelerations, i.e., with a dampened oscillatory pattern, may be peculiar to the His-Purkinje system and radically different from the pattern of response of the ventricle. Of note, however, these investigators used mean baseline cycle lengths of 750 msec (range 600 to 1000) and a mean new shorter cycle length of 475 (range 400 to 600). The mean VERP determined after 6 beats of the baseline cycle length used in their study was \(236 \pm 19\) msec. It is therefore not surprising that Tchou et al. observed no oscillation in the VERP, which in this study could only be demonstrated at considerably shorter new cycle lengths that approximated the VERP of the baseline cycle length. Given the markedly longer duration and different shape of the action potential associated with Purkinje fibers, it is also not surprising that oscillations in refractoriness might occur at much longer cycle lengths than in ventricular muscle. It is not known whether there exists, as demonstrated for
ventricle myocardium in this study, a direct relationship between the increment by which the new cycle length exceeds the effective refractory period of the His-Purkinje system and the development and amplitude of oscillation in His-Purkinje refractoriness.

**Clinical implications.** Oscillations in ventricular myocardial refractoriness may be responsible for termination of arrhythmias. Tachycardia termination is frequently successful only when multiple, closely coupled extrastimuli are introduced. The sudden acceleration in rate will result in oscillations in refractoriness that may cause conduction block and tachycardia termination. Furthermore, Spear and Moore have demonstrated that during the continuous oscillations in action potential duration observed with stimulation at rapid frequencies, a properly timed premature stimulus could either result in a dampening or an accentuation of the oscillations. The response is dependent on the coupling interval of the premature stimulus and whether the premature stimulus is delivered at the time of the long (dampening) or short (accentuation) action potential. Recording of a monophasic action potential obtained with the use of a suction or contact electrode, which reflects duration of refractoriness, may be helpful in the identification of the presence of oscillations in action potential duration and refractoriness during a tachycardia. Recognition of these oscillations may allow for selection of the appropriately timed extrastimulus to rapidly effect tachycardia termination.

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