Effect of the Intertrain Pause on the Ventricular Effective Refractory Period Measured by the Extrastimulus Technique

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MORADY, F., ET AL.: Effect of the Intertrain Pause on the Ventricular Effective Refractory Period Measured by the Extrastimulus Technique. *This study determined the effect of the duration of the intertrain pause on the ventricular effective refractory period (VERP) measured by the extrastimulus technique using conventional eight-beat basic drive trains. In 50 subjects, the VERP was measured using a basic drive train cycle length of 500 msec, 2-msec steps in the extrastimulus coupling interval, and intertrain pauses of 0, 1, 4, 8, 20, 40, 60, or 180 seconds. The VERP increased significantly with each stepwise increment in the intertrain pause up to 20 seconds, then reached a plateau. The VERP measured with an intertrain pause of 20 seconds was a mean of 13 msec longer than when measured with a conventional 4-second pause. The results of this study demonstrate a direct relationship between the VERP and the duration of the pause separating the eight-beat basic drive trains used to measure the VERP. When the cycle length of the basic drive train is 500 msec, the VERP lengthens as the duration of the intertrain pause increases from 1 to 20 seconds, demonstrating that the basic drive trains exert a cumulative effect on the VERP when the intertrain pause is shorter than 20 seconds. A cumulative effect of the basic drive trains on the VERP is lost when the intertrain pause is 20 seconds or more. (PACE, Vol. 13, April 1990)*

ventricular refractoriness, intertrain pause

Introduction

The ventricular effective refractory period (VERP) conventionally has been measured using a ventricular extrastimulus (S_2) introduced after basic drive trains that are eight beats in duration and separated by an intertrain pause of 2–5 seconds.[1–5] Because the basic drive train cycle length is usually 400–600 msec and the spontaneous sinus cycle length is typically in the range of 840 msec, the conventional technique for measuring refractoriness is associated with frequent, abrupt changes in heart rate. Whenever the heart rate increases or decreases, several minutes may be required for complete adaptation of action potential duration and ventricular refractoriness to the change in rate.[6–10] Therefore, when the basic drive is eight beats and the intertrain pause is only 2–5 seconds, there is incomplete adaptation of ventricular refractoriness to both the basic drive train cycle length and the sinus cycle length. Because the duration of the pause would be expected to influence the extent to which action potential duration adapts to the sinus cycle length, the duration of the pause could affect the measured VERP.

The purpose of this study was to determine the effect of the duration of the intertrain pause on the VERP measured by the extrastimulus technique using conventional eight-beat basic drive trains.

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Methods

Subjects Studied

The subjects of this study were 50 patients who underwent a clinically-indicated electrophysiology test for the evaluation of ventricular tachycardia, supraventricular tachycardia or unexplained syncope. Selection criteria included the presence of sinus rhythm and the absence of inducible ventricular or supraventricular tachycardia during programmed ventricular stimulation with S_2. There were 32 men and 18 women and their mean age was 58 ± 14 years (± standard deviation). Twenty-one subjects had coronary artery disease and three had a dilated cardiomyopathy, and the mean left ventricular ejection fraction in these subjects was 0.36 ± 0.10. Twenty-six subjects had no evidence of structural heart disease and had a normal left ventricular ejection fraction. The mean sinus cycle length was 851 ± 145 msec (range 650–1200 msec).

Electrophysiological Testing

Electrophysiology studies were performed in the fasting, unsedated state after informed consent was obtained and at least five half-lives after discontinuation of antiarrhythmic drug therapy. Three or four quadripolar electrode catheters (1-cm interelectrode distance) were inserted into a femoral or subclavian vein and positioned in the heart as clinically indicated. Leads V_1, I, and III and the intracardiac electrograms were recorded at a paper speed of 25–100 mm/sec on a Siemens-Elema Mingograf-7 recorder (Siemens-Elema, Solna, Sweden). Pacing was performed with a programmable stimulator (Bloom Associates, Ltd., Narbeth, PA, USA) using stimuli that had a duration of 2 msec and a current strength of twice the late diastolic threshold.

Study Protocol

The study protocol was approved by the Human Research Committee and was performed either before or after the clinically indicated portion of the electrophysiology test. A quadripolar electrode catheter was positioned against the right ventricular apex under fluoroscopic guidance and the distal two electrodes were used for bipolar pacing. The mean stimulation threshold was 0.5 ± 0.1 mA, with the stimulation threshold being 0.7 mA or less in every subject.

The study protocol consisted of measuring the VERP after 3 minutes of continuous pacing without a pause (referred to as the "steady-state" VERP) then using eight-beat basic drive trains separated by intertrain pauses ranging between 1 second and 3 minutes. In order to avoid overly lengthy studies in individual subjects, the protocol was divided into three segments and each segment was performed in a separate group of 15–20 subjects.

The first segment of the protocol was performed in 15 subjects. The steady-state VERP was measured by introducing S_2 after 3 minutes of continuous ventricular pacing at a cycle length of 500 msec. The S_2 was positioned initially at a coupling interval shorter than the VERP and was introduced after every eighth basic drive beat, with no interruption in the basic drive train by a pause; the S_2 coupling interval was increased in steps of 2 msec until ventricular capture occurred. The VERP was defined as the longest S_2 coupling interval that failed to evoke a ventricular response. Incremental S_2 coupling intervals were used to measure the VERP in order to avoid the artifactual shortening of the VERP that may occur when S_2 is positioned initially outside the VERP and the coupling interval is decreased till ventricular capture is lost.[11]

In these 15 subjects, the VERP also was measured using conventional eight-beat basic drive trains at a cycle length of 500 msec and intertrain pauses of 1, 4, 8, and 60 seconds. Determinations of the VERP were separated by a rest period of at least 1 minute and were preceded by a 1-minute conditioning period during which basic drive trains were introduced without S_2, using the same intertrain pause used to measure the VERP. In order to maximize the reproducibility of the VERP measurements, the first beat of the basic drive train was synchronized to occur 500 msec after the preceding sinus beat and a constant atrioventricular relationship was maintained by simultaneous atrial and ventricular pacing in subjects who did not have 1:1 ventriculoatrial conduction during the basic drive train.[12]

The first part of this study demonstrated a significant lengthening of the VERP when the intertrain pause was increased from 8 seconds to 1 minute, and the aim of the second segment of the protocol was to determine if lengthening the pause beyond 1 minute results in any additional increase in the VERP. In 15 subjects, the VERP was measured with the techniques described above using intertrain pauses of 4 seconds, 1 minute and 3 minutes.

No difference in the VERP was found when the intertrain pause was lengthened from 1 minute to 3 minutes, and the third segment of this study was aimed at estimating the duration of the pause associated with maximum lengthening of the VERP. The VERP was determined in 20 subjects using intertrain pauses of 8, 20, 40, and 60 seconds.

Analysis of Data

The VERPs were analyzed using a repeated measures analysis of variance. Multiple comparisons were performed using Fisher's Least Significant Difference multiple comparisons procedure and a pooled estimate of variance from the three segments of the study. A P value < 0.05 was considered significant.

Results

The steady-state VERP and the VERPs measured using intertrain pauses of 1, 4, 8, and 60 seconds in 15 subjects are shown in Table I. The mean steady-state VERP was 227 ± 12 msec. The VERP increased significantly as the duration of the intertrain pause lengthened progressively from 1 to 60 seconds (P < 0.001 for each consecutive paired comparison).

The VERPs measured in 15 subjects using intertrain pauses of 4, 60, and 180 seconds were 240 ± 13, 253 ± 15, and 253 ± 16 msec, respectively. The VERPs measured with pauses of 60 and 180 seconds were significantly longer than the VERP measured with a 4-second pause (P < 0.001), but did not differ from each other.

The VERPs measured in 20 subjects using intertrain pauses of 8, 20, 40, and 60 seconds are shown in Table II. The VERP increased significantly when the duration of the intertrain pause increased from 8 to 20 seconds (P < 0.001), then remained unchanged as the pause increased to 40 and 60 seconds.

Table I.

Ventricular Effective Refractory Periods Measured Using Intertrain Pauses of 0–60 Seconds in 15 Subjects

Duration of Intertrain Pause (sec)	VERP (msec, Mean ± SD)
0*	227 ± 12
1	240 ± 12†
4	242 ± 13†
8	249 ± 14†
60	257 ± 15†

* VERP measured after 3 minutes of continuous ventricular pacing; †P < 0.001 in comparison to preceding pause duration. Abbreviations: SD = standard deviation; VERP = ventricular effective refractory period.

Table II.

Ventricular Effective Refractory Periods Measured Using Intertrain Pauses of 8–60 Seconds in 20 Subjects

Duration of Intertrain Pause (sec)	VERP (msec, Mean ± SD)
8	248 ± 14
20	255 ± 14†
40	256 ± 14††
60	258 ± 15††

† P < 0.001 compared to preceding pause duration; ††P > 0.05 compared to preceding pause duration. Abbreviations as in Table I.

Discussion

The results of this study demonstrate that the duration of the intertrain pause has a direct relationship to the VERP measured using conventional eight-beat basic drive trains. When the cycle length of the basic drive train is 500 msec, the VERP lengthens by an average of 15 msec as the duration of the intertrain pause is increased from 1 to 20 seconds. However, when the intertrain pause is increased beyond 20 seconds, there is no additional lengthening of the VERP.

In this study the mean sinus cycle length was approximately 850 msec, and the cycle length of the basic drive train was 500 msec, which is representative of the 400–600 msec basic drive cycle lengths typically used during clinical electrophysiology studies. Therefore, during determinations of the VERP, every few seconds the ventricular cycle length changed by an average of 350 msec. Prior experimental and clinical studies have demonstrated that when there is an abrupt decrease in cycle length, up to several minutes are required before the action potential duration and refractory period of ventricular muscle adapt completely to the new cycle length.[6–10] When the drive train is only eight beats in duration, there is only partial adaptation to the cycle length of the basic drive train, explaining why the use of intertrain pauses even as short as 1 second resulted in a VERP that was on the average at least 13 msec longer than when a continuous 3-minute basic drive train was used.

Prior experimental studies have demonstrated that an abrupt increase in cycle length also requires several minutes before complete adaptation of action potential duration to the new cycle length occurs.[8] Therefore, if the intertrain pause separating the eight-beat drive trains is short, the action potential duration of ventricular muscle may not return to its original baseline value before the onset of the next basic drive train. In this event the basic drive trains would be expected to exert a cumulative effect on ventricular refractoriness, resulting in progressive shortening of the VERP as the intertrain pause is decreased, as observed in this study. The results of this study indicate that when the ventricular basic drive train is eight beats in duration and has a cycle length of 500 msec, an average of 20 seconds of sinus rhythm is required for complete readaptation of ventricular refractoriness to the sinus cycle length. Our results demonstrate that a cumulative effect of the basic drive trains on ventricular refractoriness is lost only when the intertrain pause is at least 20 seconds.

Limitations

A limitation of this study is that, because of time constraints, only one basic drive train cycle length was used to measure the VERP. In the only other study that examined the effect of the intertrain pause on the VERP, the basic drive cycle length was 600 msec and intertrain pauses of 1 to 20 seconds were used;[11] in concert with the results of the present study, the VERP was found to lengthen significantly as the duration of the pause increased. Therefore, it is likely that the qualitative relationship found in this study between the intertrain pause and the VERP is applicable to basic drive train cycle lengths other than 500 msec. However, it is unlikely that the quantitative findings of this study could be applied to a wide range of drive cycle lengths.

Because of technical limitations, the sinus cycle length was not controlled during the pauses separating the basic drive trains. For this reason, there was inter-subject variability in the sinus cycle length and there may also have been some degree of intra-subject variability in the sinus cycle length between the basic drive trains. Therefore, a variable that influenced the abrupt changes in cycle length that occurred during the determinations of the VERP was not controlled.

It should be noted that the only pause durations between 8 and 60 seconds tested in this study were 20 and 40 seconds. Given this fact along with the intra-subject variability in the sinus cycle length, it must be recognized that 20 seconds is only an estimate of the minimum pause duration at which a plateau effect on the VERP is reached.

Clinical Implications

With the standard intertrain pause of 2–5 seconds typically used during clinical electrophysiology studies, the basic drive trains exert a cumulative effect on the VERP and therefore the VERP may be influenced by the number of basic trains preceding the S_2 coupling interval that defines the VERP. Therefore, to improve reproducibility in the measurement of refractoriness, it is appropriate to have a conditioning period during which the eight-beat basic drive trains are introduced without an extrastimulus, before actual measurement of the VERP. In this study, a 1-minute conditioning period was used, however the minimum duration of the conditioning period required to attain the maximum cumulative effect of the basic drive trains on the VERP was not determined. The minimum number of basic drive trains needed to attain the maximum cumulative effect on the VERP is likely to depend on the cycle length of the basic drive train and the duration of the intertrain pause.

Another implication of the results of this study is that a pause longer than the typical 2–5 second intertrain pause is necessary if the aim is to determine the effect of a particular drive train duration on the VERP. At a drive train cycle length of 500 msec, if a pause shorter than 20 seconds is used, the VERP will be affected not only by the number of beats in the drive train, but also by the total number of drive trains.

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References

1. Kowey PR, Folland ED, Parisi AF, et al. Programmed electrical stimulation of the heart in coronary artery disease. Am J Cardiol 1983; 51:531–536.
2. Estes NAM, Garan H, McGovern B, et al. Influence of drive cycle length during programmed stimulation on induction of ventricular arrhythmias: Analysis of 403 patients. Am J Cardiol 1986; 57:108–112.
3. Cooper MJ, Koo CC, Skinner MP, et al. Comparison of immediate versus day to day variability of ventricular tachycardia induction by programmed stimulation. J Am Coll Cardiol 1989; 13:1599–1607.
4. Morady F, Kou WH, Kadish AH, et al. Effect of basic drive train cycle length on induction of ventricular tachycardia by a single extrastimulus. J Electrophysiol 1989; 3:111–116.
5. The ESVEM Investigators. Electrophysiologic study versus electrocardiographic monitoring for selection of antiarrhythmic therapy of ventricular tachyarrhythmias. Circulation 1989; 79:1354–1360.
6. Janse MJ, van der Steen ABM, Van Dam RTH, et al. Refractory period of the dog's ventricular myocardium following sudden changes in frequency. Circ Res 1969; 24:251–262.
7. Boyett MR. An analysis of the effect of the rate of stimulation and adrenaline on the duration of the cardiac action potential. Pflugers Arch 1978; 377:155–166.
8. Boyett MR, Jewell BR. Analysis of the effects of changes in rate and rhythm upon electrical activity in the heart. Prog Biophys Mol Biol 1980; 36:1–52.
9. Gibbs CL, Johnson EA. Effect of changes in frequency of stimulation upon rabbit ventricular action potential. Circ Res 1981; 9:165–170.
10. Morady F, Kadish AH, Toivonen LK, et al. The maximum effect of an increase in rate on human ventricular refractoriness. PACE 1988; 11:2223–2234.
11. Morady F, Kadish AH, Kushner JA, et al. Comparison of ventricular refractory periods determined by incremental and decremental scanning of an extrastimulus. PACE 1989; 12:546–554.
12. Kadish A, Toivonen L, Kushner J, et al. Factors that influence the reproducibility of ventricular refractoriness. J Am Coll Cardiol 1989; 13:45A. Abstract