Effects of Sudden Change in Cycle Length on Human Atrial, Atrioventricular Nodal and Ventricular Refractory Periods

ISAAC WIENER, M.D., STEVEN KUNKES, M.D., DAVID RUBIN, M.D., JOEL KUPERSMITH, M.D., MILTON PACKER, M.D., ROBERTA PITCHON, R.N., AND PAUL SCHWEITZER, M.D.

SUMMARY In the steady state, the refractory periods of the human atrium, atrioventricular (AV) node, and ventricle are a function of cycle length. We compared the change in refractoriness that occurred when these refractory periods were measured after eight beats at a shorter cycle length with the change that occurred when these refractory periods were measured after a single beat at the shorter cycle length. For a decrease in cycle length of 235 ± 63 m sec, the atrial effective refractory period shortened 31 ± 24 m sec (p < 0.01) when measured after eight beats at the shorter cycle length and 26 ± 24 m sec (p < 0.01) when measured after a single beat at the shorter cycle length. Similar changes were seen in atrial functional refractory period. For a decrease in cycle length of 214 ± 63 m sec, the AV nodal effective refractory period increased 30 ± 39 m sec (p < 0.05) when measured after eight beats and 31 ± 34 m sec (p < 0.05) when measured after a single beat. The AV nodal functional refractory period showed moderate shortening with decreases in cycle length, both when measured after eight beats and when measured after a single beat (p = NS). For both the atrium and AV node, there was no significant difference between the change in refractoriness after a single beat at the shorter cycle length and after eight beats at the shorter cycle length. For a decrease in cycle length of 175 ± 52 m sec, the ventricular effective refractory period shortened 26 ± 10 m sec (p < 0.01) when measured after eight beats and 16 ± 12 m sec (p < 0.01) when measured after a single beat at the shorter cycle length. Thus, a single beat at the shorter interval produced 60% of the shortening of refractoriness produced by eight beats at the shorter interval (p < 0.01). These findings have implications for the performance and interpretation of stimulation studies and provide insight into the mechanism of initiation of tachycardia by premature beats.

REFRACTORINESS of cardiac tissue is a function of cycle length. This relationship, first recognized in isolated heart tissue, has subsequently been shown in both the canine and human atrium, atrioventricular (AV) node and ventricles.4-6 There is some controversy as to whether changes in refractory periods in the canine heart occur after a single beat at the new cycle length or represent a cumulative effect of multiple beats at the new cycle length.5-6,7 There are no data in humans on whether cycle-length-dependent changes in refractoriness are seen after a single beat at the new cycle length. In this report, we describe the effects of sudden changes in cycle length on the refractory period of the human atrium, AV node and ventricle.

Methods

Patients

There were 23 males and seven females, average age 49.9 ± 19 years. Six patients had atherosclerotic cardiovascular disease, four had cardiomyopathy, two had hypertensive heart disease, one patient had...
rheumatic heart disease and one had congenital heart disease; 16 patients had no organic heart disease. Indications for electrophysiologic study included ventricular tachycardia in 10 patients, bradyarrhythmia or AV block in eight, supraventricular tachycardia in four and syncope of unknown etiology in eight.

Electrophysiologic Studies

The effects of cycle length on refractoriness were studied during clinical electrophysiologic studies performed after informed consent was obtained. All antiarrhythmic drugs were discontinued five half-lives before the study. Using the Seldinger technique and fluoroscopic guidance, we introduced a 6F quadripolar catheter into the high right atrium for pacing and recording, a 6F tripolar catheter into the area of the tricuspid valve for recording the His potential, and a 4F bipolar catheter into the right ventricular apex for pacing.

Electrocardiographic leads I, II and III, the bipolar electrogram from the high right atrial catheter and a bipolar electrogram from the His bundle catheter were amplified on an Electronics for Medicine DR-12 recorder and recorded on photographic paper at a paper speed of 100 mm/sec. Pacing impulses were generated by a digitally programmed stimulator (Bloom Associates, Ltd.). Impulses 1.5 msec wide and twice diastolic threshold were used throughout.

The refractory periods of the high right atrium, AV node and ventricle were determined by the extrastimulus technique. An extrastimulus was induced and moved progressively closer to the preceding beat in 5-10-msec increments. The refractory period was determined after eight beats at a constant basic cycle length, eight beats at a shorter constant basic cycle length, and eight beats at the longer constant basic cycle length, followed by a single premature beat at a coupling interval equal to the shorter basic cycle length. Continuous recordings were used to document that each of the eight beats of the constant basic cycle length captured and that there was no intermittent failure to capture or no premature beats.

In the ventricle, an additional protocol was performed. First, the ventricular effective refractory period was determined after eight beats at a constant basic cycle length. Then, an extrastimulus (S2) was introduced with a coupling interval 10–20 msec longer than the refractory period of the eighth beat. The effective refractory period of this S2 was measured. Finally, an S2 with a longer coupling interval of 350–450 msec was introduced after eight beats at the same constant basic cycle length. The refractory period of this S2 was then determined.

Definitions

The atrial effective refractory period was defined as the longest S1S2 interval that did not capture the atrium. The atrial functional refractory period was defined as the shortest A1A2 achieved. The AV nodal effective refractory period was defined as the longest A1A2 (measured in the His bundle lead) that did not conduct to the His bundle. The AV nodal functional refractory period was defined as the shortest H1H2 achieved. The ventricular effective refractory period was defined as the longest S2S2 that did not capture the ventricle. For the AV node, only patients in whom all measurements could be determined were included. Patients in whom any of the measurements were limited by atrial refractoriness or who developed AV nodal Wenckebach at one of the basic cycle lengths were excluded.

Statistical Analysis

Statistical significance was determined by analysis of variance using Duncan's multiple-comparison procedure for detecting differences between mean responses.

Results

Atrium

Results for the atrium are shown in figure 1. For a mean decrease in cycle length of 235 ± 63 msec, the atrial effective refractory period shortened 31 ± 24 msec (p < 0.01) when measured after eight beats at the shorter cycle length and 26 ± 24 msec (p < 0.01) when measured after a single beat at the shorter cycle length. There was no statistical difference between the degree of shortening after a single beat and the degree of shortening after eight beats.

![Figure 1. Effects of changes in cycle length on the atrial effective refractory period (ERP)]. In each panel, cycle length (msec) is the abscissa and ERP (msec) is the ordinate. Each dot represents the refractory period of a given patient measured at that basic cycle length. (A) Lines connect refractory period measurements after eight beats at a long cycle length and after eight beats at a shorter cycle length. (B) Lines connect refractory period measurements after eight beats at a long cycle length and after a single beat at the same short cycle length as in panel A. There was no significant difference between the degree of shortening of refractoriness after eight beats at the shorter cycle length and the degree of shortening of refractoriness after a single beat at the shorter cycle length.
For a mean decrease in cycle length of 235 ± 63 msec, the atrial functional refractory period shortened 27 ± 19 msec (p < 0.01) when measured after eight beats at the shorter cycle length and 25 ± 19 msec (p < 0.01) when measured after a single beat at the shorter cycle length. There was no statistical difference between the degree of shortening after a single beat and the degree of shortening after eight beats.

AV Node

Results for the AV node are shown in Figure 2. For a mean decrease in cycle length of 214 ± 63 msec, the AV nodal effective refractory period lengthened 30 ± 39 msec (p < 0.05) when measured after eight beats at the shorter cycle length and 31 ± 34 msec (p < 0.05) when measured after a single beat at the shorter cycle length. There was no significant difference between the degree of lengthening after a single beat at the shorter cycle length and after eight beats at the shorter cycle length.

For a mean decrease in cycle length of 214 ± 63 msec, the AV nodal functional refractory period shortened 14 ± 18 msec (p = NS) when measured after eight beats at the shorter cycle length and 10 ± 21 msec (p = NS) when measured after a single beat at the shorter cycle length. The functional refractory period after a single beat at the shorter cycle length did not differ from that after eight beats at the shorter cycle length.

Ventricle

Results for the ventricle are shown in Figure 3. In 14 patients, for a mean decrease in cycle length of 175 ± 52 msec, the ventricular effective refractory period decreased 26 ± 10 msec (p < 0.01) after eight beats at the shorter cycle length and 16 ± 12 msec (p < 0.01) after a single beat at the shorter cycle length. Thus, after a single beat, 60% of the shortening seen after eight beats was elicited. The difference in shortening between one beat and eight beats was statistically significant (p < 0.01).

In 17 patients, at 27 different basic cycle lengths, the effective refractory periods of single extrastimuli at two different coupling intervals were compared. In each case, the effective refractory period of the extrastimulated beat with the longer coupling interval was longer than the effective refractory period of the extrastimulated beat with the shorter coupling interval. For an extrastimulated beat with an average coupling interval of 411 ± 35 msec, the mean effective refractory period was 219 ± 28 msec (p < 0.01 vs effective refractory period at the basic cycle length), while for an extrastimulated beat with an average coupling interval of 249 ± 29 msec, the mean effective refractory period was 174 ± 29 msec (p < 0.01 vs extrastimulated beat with longer interval).

Discussion

Denes et al. showed that in the human heart, as cycle length is decreased, atrial effective and functional

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Effects of changes in cycle length on the atrio-ventricular nodal effective refractory period (ERP). Format is the same as in figure 1. (A) Lines connect refractory period measurements after eight beats at a long cycle length and after eight beats at a shorter cycle length. (B) Lines connect refractory period measurements after eight beats at a long cycle length and after a single beat at the same short cycle length as in panel A. There was no significant difference between the degree of lengthening of refractoriness after eight beats at the shorter cycle length than the degree of lengthening of refractoriness after a single beat at the shorter cycle length.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Effects of changes in cycle length on the ventricular effective refractory period (ERP). Format is the same as in figure 1. (A) Lines connect refractory period measurements after eight beats at a long cycle length and after eight beats at a shorter cycle length. (B) Lines connect refractory period measurements after eight beats at a long cycle length and after a single beat at the same short cycle length as in panel A. There was significantly more shortening of refractoriness after eight beats at the shorter cycle length than after a single beat at the shorter cycle length.
refractory periods shorten, the AV nodal effective refractory period lengthens, and the AV nodal functional refractory period shortens slightly. Guss et al.\textsuperscript{8} found that the effective refractory period of the human ventricle shortens with decreases in cycle length. Denes et al. studied refractoriness after 10 driven beats at a constant cycle length and Guss et al. used eight to 12 beats at a constant cycle length.

Our findings confirm the results of Denes et al. and Guss et al. We also studied the effects of a single beat at a shorter cycle length. For the atrium and AV node, the changes after a single beat were of the same magnitude as those seen after eight beats at the shorter cycle length. For the ventricle, the change after a single beat was 60\% of the change seen after eight beats.

Several animal studies have relevance to our findings. Mendez et al.\textsuperscript{3} concluded that, in canine atrial tissue, refractoriness varied with the immediately preceding interval, while Han and Moe\textsuperscript{7} found a cumulative effect of cycle length on atrial refractoriness in three of four dogs. Possible explanations for this disparity are that Mendez et al. introduced premature beats after a basic drive of six beats and attributed significance only to changes of 5\%–10\% of baseline. Han and Moe used a basic drive of up to 16 beats and attributed significance to smaller changes. Our methods and conclusions are close to those of Mendez et al. We introduced premature beats after a basic drive of eight beats because this is the number commonly used in clinical electrophysiologic studies. It is possible that the number does not represent a steady state and further shortening would occur with a longer basic drive. Recent data from studies in isolated tissue suggest that a true steady state of action potential duration, a measure related to effective refractory period, may not be achieved before 3 minutes at the same rate.\textsuperscript{9}

Studies of the canine AV nodal functional refractory period give conflicting results as to the influence of the immediately preceding cycle length.\textsuperscript{6,7} These studies have limited relevance to our study because denervated canine models were used and because the effective refractory period was not measured. The functional refractory period is also affected by conduction time and therefore may not be as accurate a measure of refractoriness as the effective refractory period.\textsuperscript{8}

Simson et al.,\textsuperscript{11} using a denervated canine preparation, reported a cumulative effect of cycle length on the AV nodal effective refractory period during AV nodal Wenckebach cycles and after a blocked premature beat during stressed 1:1 conduction. These workers found that this cumulative effect was related to the frequency of stimulation, and was not seen at the cycle lengths used in our study.\textsuperscript{11}

In the canine ventricle, Mendez et al.\textsuperscript{9} reported that the functional refractory period was dependent on the preceding cycle length, while both Janse et al.\textsuperscript{4} and Han and Moe\textsuperscript{7} found that both the effective and functional refractory periods represented a cumulative effect of many cycle lengths. Our results support a cumulative effect of cycle length on the human ventricular effective refractory period.

Our results have implications for the performance and interpretation of stimulation studies. During these studies, the heart is generally driven at a constant cycle length for eight to 10 beats, after which premature beats are introduced. Spontaneous ectopy sometimes makes it difficult to achieve this steady state. Our data suggest that fewer beats at the given cycle length may give refractory period determinations similar to those found after a longer basic drive in the atrium and AV node, but not in the ventricle. However, properties other than local refractoriness (i.e., conduction time and dispersion of refractoriness) may be different after single beats than after pacing. Our finding that extra-stimulated beats with shorter coupling intervals have shorter refractory periods than those with longer coupling intervals suggests that if S1S2S3 stimulation is used to "peel back" refractoriness, S2 should be set close to the refractory period of S1.

References

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Circulation. 1981;64:245-248
doi: 10.1161/01.CIR.64.2.245

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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