Effects of Abrupt Changes in Cycle Length on Refractoriness of the His-Purkinje System in Man

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SUMMARY Abrupt changes in cycle length (CL) occur frequently in the clinical setting of atrial fibrillation. However, the effects of such changes on the His-Purkinje system (HPS) have not previously been considered during aberrant ventricular conduction (VAb). In 12 patients who manifested VAb with atrial premature stimulation (A₂) during sinus rhythm, the relative refractory period (RRP) of the HPS was evaluated during a constant atrial CL (method I) and during abrupt changes in the CL (method II), wherein the A₂ was coupled to an atrial CL (last A₁A₁) comparable to method I. This last A₁A₁ during method II was preceded by a series of constant atrial CLs 100–200 msec longer (method IIIA) in 11 of 12 patients, or 100–300 msec shorter (method IIB) in all 12 patients. Although abrupt changes in the atrial CL using method IIA resulted in a longer HH interval (by 0–30 msec; mean 13.2 ± 9.2 msec) preceding the A₂, the RRP-HPS was 5–20 msec shorter (mean 9.3 ± 5.3 msec) compared with method I in eight patients. The effect of abrupt changes was further evaluated in nine patients using method III, with a constant atrial CL, with a duration equal to the last H₂H₂ interval of method IIA. The VAb that occurred with method III was not manifested with method IIA in seven of nine patients, and in two patients the RRP-HPS was the same or less. Conversely, method IIB resulted in a shorter HH interval (by 0–110 msec; mean 28.9 ± 21.1 msec) preceding A₂, but in 10 patients, RRP-HPS was 5–40 msec longer (mean 20.7 ± 10.5 msec) than that of method I and in two, VAb was only manifested using method IIB. Further scanning with method III, derived from the HH interval immediately preceding A₂ of method IIB, was performed in seven patients and compared with method IIB. Prolongation in the RRP-HPS was shown using the latter method. The results indicate that abrupt changes in CL influence the functional behavior of the HPS in a manner not anticipated. Such changes may have important implications in determining the occurrence of VAb during atrial fibrillation.

THE PHENOMENON of aberrant ventricular conduction (VAb) during antegrade propagation of premature supraventricular impulses has been recognized for many decades.1–7 The classic paper by Gouaux and Ashman described the occurrence of VAb during atrial fibrillation in association with the sequence of a long cycle length (CL) followed by short CL.1 Intracardiac electrophysiologic techniques and His bundle electrogram recordings have demonstrated that such VAb is a result of functional conduction delay in the His-Purkinje system (HPS) and have confirmed the physiologic relationship between CL and VAb: a long CL followed by an antegradely propagated premature supraventricular impulse favors the occurrence of VAb, while a short CL decreases the likelihood of VAb:8–13 that is, the relative refractory period (RRP) of the HPS varies directly with CL.

Such refractory period determinations are usually performed during a constant CL or sinus rhythm and do not consider the varying CL pattern characteristic of atrial fibrillation.5–13 Although varying CL provides the setting for long CL–short CL sequences and, therefore, engenders the occurrence of VAb, the effect, if any, on VAb of variation in the cycle length preceding (CL₁) the long CL has not been determined. We studied the effects on the functional properties of the HPS of varying CL₁. In this report, we discuss several new findings and their clinical implications.

Materials and Methods

The 12 patients (six males and six females, ages 22–77 years) included in this series were studied for a variety of reasons, including palpitations, syncope and previously suspected or documented tachyarrhythmias. The underlying structural heart disease was arteriosclerotic in four, primary myocardial in two and valvular in one. Five patients had no detectable structural heart disease. Electrophysiologic studies were performed in the postabsorptive, unsedated state.8 The nature of the procedure was explained and each patient gave signed consent. Under local anesthesia, multipolar electrode catheters were introduced percutaneously and, with fluoroscopic guidance, were positioned in the high right atrium, atrioventricular junction, and right ventricle to record local electrical activity or for local pacing. All intracardiac electrograms (filter frequency 30–500 Hz), three surface ECG leads (I, II and V₁) and time lines were simultaneously displayed on a multichannel oscilloscope and recorded on magnetic tape. Programmed electrical stimulation was accomplished with a digital stimulator delivering rectangular impulses with adjustable amplitude and duration. All equipment was grounded. Patients were electrically isolated during the studies.

Patients were studied with the conventional technique of atrial premature stimulation (A₂), designated as method I (fig. 1), wherein the A₂ was introduced after a series of six atrial beats of predetermined CLs (A₁A₁). To evaluate the effect of abrupt variation in CL on aberrant conduction, all patients were also studied.

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METHOD I: \( CL_p = CL_R \)

\[ A_1 \] \( \begin{array}{c} CL_p \ \ A_1' \ \ CL_p \end{array} \) \( A_1 \) \( A_1' \)

METHOD II A: \( CL_p > CL_R \)

\[ A_1 \] \( \begin{array}{c} CL_p \ \ A_1' \ \ CL_p \ \ A_1 \end{array} \) \( A_1 \) \( A_1' \)

METHOD II B: \( CL_p < CL_R \)

\[ A_1 \] \( \begin{array}{c} CL_p \ \ A_1' \ \ CL_p \ \ A_1 \ \ CL_R \end{array} \) \( A_1 \) \( A_1' \) \( A_1 \)

FIGURE 1. Stimulation protocols. The main difference between methods I and II is that in method I the \( A_1 \) is preceded by a series of constant atrial CLs, whereas in method II the CL just before \( A_1 \) is abruptly altered \((A_1A_1')\) compared with the preceding CLs \((A_1A_1)\). In all methods, the reference CL \((CL_{R})\) is the atrial CL to which \( A_1 \) is coupled, whereas the CLs preceding the \( CL_p \) are designated as \( CL_p \). In method IIA, the \( CL_p > CL_R \), whereas in method IIB, the \( CL_p < CL_R \). In method I, \( CL_p = CL_R \).

with method II (fig. 1), in which, after a series of constant atrial CLs, the last \( A_1A_1 \) (i.e., immediately preceding the \( A_2 \)) was altered. The data presented here include analysis of the effect on aberrant conduction of both the last and next-to-last \( A_1A_1 \) cycles; therefore, the two are designated differently to avoid confusion. The last \( A_1A_1 \) cycle during both methods I and II is designated as the reference CL \((CL_{R})\); all CLs preceding the \( CL_q \) are called \( CL_p \). The stimulation technique of method II is further divided into A and B (fig. 1), depending on whether the \( CL_q \) was larger or smaller. All \( A_1A_1 \) cycles preceding the \( CL_q \) are of the same duration and equal \( CL_p \) (fig. 1). In the schema and tracings, the atrial and His deflections of the altered CL \( CL_q \) of method II are depicted as \( A_1\); \( A_1' \) and \( H_1 \); \( H_1' \) for a clearer separation from all other constant CLs.

With method II, by pacing design, only the atrial (rather than HH) CL could be altered from \( CL_p \) to \( CL_R \). However, the occurrence of aberrant conduction relates to the HH rather than the AA CL unless the two are identical. The \( A_1\); \( A_1' \) equals \( H_1 \); \( H_1' \) with method I and also during the \( CL_p \) of method II, but not during the \( CL_q \) of method II. How the \( A_1\); \( A_1' \) during \( CL_q \) of method II \((A_1A_1')\) could differ from the corresponding \( H_1 \); \( H_1' \) CL is shown in figure 2. The terms \( CL_p \) and \( CL_q \) refer only to the atrial CL, whereas the corresponding HH CLs are depicted as \( CL_p\); HPS and \( CL_q\); HPS. For a given \( CL_q \), a longer \( CL_p \) lengthens \( CL_q\); HPS and a shorter \( CL_p \) shortens \( CL_q\); HPS. The amount of change is equal to the difference in AH intervals between \( CL_p \) and \( CL_q \). Therefore, although the atrial CL \( CL_q \) of method I measuring exactly equal to the atrial \( CL_q \) of methods IIA and IIB was available in all patients, due to small but definite differences between atrial \( CL_q \) and corresponding \( CL_p\); HPS during method II, additional atrial CLs were scanned; these are referred to as method III (fig. 3). This was done in order to obtain a constant \( H_1 \); \( H_1' \) CL equal to the \( H_1 \); \( H_1' \) interval of methods IIA and IIB. During method III, the \( A_1\); \( A_1' \) and \( H_1 \); \( H_1' \) CLs are constant, as in method I. However, the exact CL of method III could be derived only after obtaining the \((A_1H_1, V_1)\) values of methods IIA and IIB by direct measurement; hence the designation of method III.

Definition of Terms

\( A_1, H_1, V_1 \) — the atrial, His bundle, and ventricular depolarizations during all constant atrial CLs.

\( A_1', H_1', V_1' \) — the atrial, His bundle, and ventricular depolarizations of the altered CL just before \( A_2 \) during method II.

\( A_2, H_2, V_2 \) — the atrial, His bundle, and ventricular depolarizations resulting from coupled premature atrial stimulation.

Functional refractory period (FRP) of the atrioventricular (AV) node — the shortest \( H_1H_1' \) interval in response to any \( A_1A_2 \).

RRP of the HPS — the longest \( H_1H_1' \) interval at which \( H_1 \) conducts to the ventricles with a longer HV interval than the basic drive beat or with a QRS showing a definite bundle branch block (BBB) pattern.

Results

None of the patients had evidence of preexisting BBB, although in three cases a nonspecific intraventricular conduction defect was noted on the resting ECG. All patients manifested VAb with either premature atrial stimulation \((A_1)\) at atrial paced CLs slightly shorter than sinus CL or with \( A_2 \) coupled to sinus beats. Patients were in sinus rhythm and had normal AH and HV intervals and were not taking any cardiovascular medication at the time of study. The electrophysiologic data are listed in table 1. During VAb, a right BBB (RBBB) morphology was noted in eight patients, a left BBB (LBBB) configuration in one (patient 7), and both RBBB and LBBB morphologies in three (patients

METHOD I

\[ A_1 \] \( \begin{array}{c} H_1 \ \ CL_p \ \ CL_p - HPS \ \ A_1' \ \ H_1 \ \ CL_R \ \ CL_R - HPS \end{array} \) \( A_1 \) \( A_1' \)

METHOD II A

\[ A_1 \] \( \begin{array}{c} H_1 \ \ CL_p \ \ CL_p - HPS \ \ A_1' \ \ H_1 \ \ CL_R \ \ CL_R - HPS \end{array} \) \( A_1 \) \( A_1' \)

METHOD II B

\[ A_1 \] \( \begin{array}{c} CL_p \ \ CL_p - HPS \ \ CL_R \ \ CL_R - HPS \ \ A_1' \ \ H_1 \ \ A_1' \ \ H_1 \ \ A_1' \end{array} \) \( A_1 \) \( A_1' \)

FIGURE 2. Derivation of the corresponding His-Purkinje system (HPS) cycle length (CL) during altered \( CL_q \) of method II. The schema outlines the last two atrial CLs before \( A_2 \). The atrial CLs are labeled \( CL_p \) and \( CL_R \), whereas the corresponding \( H_1H_1' \) CLs are depicted as \( CL_p\); HPS and \( CL_q\); HPS, respectively. The altered \( CL_q \) and \( CL_q\); HPS during method II are depicted as \( A_1\); \( A_1' \) and \( H_1 \); \( H_1' \) to distinguish these from other constant CLs. Because \( A_1\); \( H_1 \) is constant, the \( CL_q = CL_q\); HPS in method I. However, with method IIA, the \( CL_q\); HPS is greater than the corresponding \( CL_q \) by the amount that \( A_1\); \( H_1' \) is longer than \( A_1\); \( H_1 \). Similarly, during method IIB the \( CL_q\); HPS is shorter than \( CL_q \) by the amount that \( A_1'\); \( H_1 \) is shorter than \( A_1\); \( H_1' \).
FIGURE 3. Derivation of method III from method II. (A) Method I. (B) Method IIA produces a decrease in A, H, of CLR in method IIA such that the CLR-HPS is now longer than CLR-HPS of method I. (C) Method III. The H, H', value in panel B is directly measured and another atrial CL of constant duration is scanned, wherein the H, H', CL = H, H' of method IIA similar to method I. All A, A', and H, H', CLs during method III are the same, but exceed the CLs of method I. (D and E) In a similar way, method III is used to obtain a constant H, H', CL to approximate H, H' of method IIB. The A, A', and H, H', CL in panel E are of the same duration but are less than those of method I.

2, 5 and 9). The pertinent data for each CL are provided in table 1.

The range in which CLR was varied was limited at longer CLs by the ability to maintain constant atrial capture without spontaneous sinus beats and at shorter CLs by the occurrence of pacing-induced AV nodal Wenckebach phenomenon. Within these limits, CLR was 100-200 msec longer than CLR or 100-300 msec shorter than CLR.

A change of atrial CL from CLR to CLR (method II) generally produced a change in CLR-HPS that did not exactly equal the atrial CLR due to a concomitant change in AV nodal (AH) conduction (fig. 2). In fact, the change in the atrial CLR resulted in reciprocal change in the corresponding HH' CL. During this study, when atrial CLR was longer than CLR (method IIA), the CLR-HPS was 0-30 msec longer (mean 13.2 ± 9.2 msec) than the corresponding atrial CLR (or CLR-HPS of method I). Likewise, when the atrial CLR was shorter than CLR (method IIB), the CLR-HPS was 0-110 msec shorter (mean 28.9 ± 21.1 msec) than the corresponding atrial CLR (or CLR-HPS of method I). The greater change in CLR-HPS at shorter CLR was attributed to a greater effect on AV nodal conduction at a shorter paced atrial CL.

Effect of a CLR Longer Than CLR on VAb (table 1)

The effect of method IIA, with which the CLR was longer than the CLR, could be compared in 11 of 12 patients (nos. 1-11) with method I (table 1). At the same atrial CLR, the RRP-HPS was 5-20 msec (mean 9.3 ± 5.3 msec) shorter with method IIA than with method I in eight patients (nos. 1-4, 7-9 and 11) (figs. 4A-C) at one or more CLs. Patients 5 and 6 showed a 10-20-msec increase in the RRP-HPS with method IIA compared with method I. In patient 10, the FRP of the AV node limited determination of the RRP-HPS during method IIA. In nine cases (patients 1-4 and 6-10), the CLR-HPS during method IIA exceeded the atrial CLR of method I by 5-30 msec despite the same atrial CLR. Method III was therefore used to approximate the H, H', CL of method IIA to detect small changes in the RRP-HPS that might have been caused by subtle variation in the HH CL between the CLR of methods I and IIA. In patients 5 and 11, the CLR-HPS with method IIA was the same as during method I and, therefore, derivation of method III was unnecessary.

Analysis of RRP-HPS showed that this variable either decreased or did not change whenever the CLR-HPS of method IIA was compared with CLR-HPS of the same but constant duration, i.e., method I or III (table 1). The shortening of RRP-HPS with method IIA was particularly noticeable in patients 1, 2, 4, 7, 8, 9 and 10 at CLR-HPS sequences of 700/500, 800/600, 800/600, 600/500, 800/600 and 650/500, where the RRP-HPS shortened to less than the FRP of
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Values listed as < under RRP-HPS represent the functional refractory period of the atrioventricular node. All electrophysiologic data are in msec.

**Abbreviations:** CL_R = atrial preceding cycle length (A1A1); CL_R = atrial reference cycle length (A1A1' or A1A1); CL_R-HPS = reference cycle length His-Purkinje system (H1H1 or H1H1'); RRP-HPS = relative refractory period of the HPS.

the AV node, and VAb could no longer be demonstrated. However, at a CL_R-HPS of the same duration with method III, VAb occurred at same or longer H1H2 intervals compared with method IIA (figs. 4E and F). Therefore, when the atrial CL was altered before A2, such that the CL_R was longer than CL_R, i.e., method IIA (figs. 2-4), three events were generally noted: (1) the H1H2' CL preceding A2 was slightly longer than if the A2 had been coupled to a series of constant CLs, i.e., CL_R = CL_R, necessitating derivation of method III for more precise comparison of RRP-HPS. (2) In individual patients, a greater difference from CL_R to CL_R produced proportionately longer difference between the atrial CL_R and CL_R-HPS. (3) Despite the longer CL_R-HPS with method IIA, the RRP-HPS was the same as or less than that with method I and, therefore, manifestation of VAb with method IIA necessitated shorter H1H2 intervals. At times, shorter H1H2 intervals could not be achieved and were limited by the AV nodal FRP (figs. 4E and F).

**Effect of a CL_R Shorter Than CL_R on VAb (Table 1)**

The influence of method IIB, with which the CL_R was shorter than the CL_R, was compared with method I in all patients at one or more basic CLs (table 1). At the same CL_R as method I, the RRP-HPS with method IIB was 5-40 msec longer (mean 20.7 ± 10.5 msec) in 10 of 12 cases (fig. 5A; compare with fig. 4A). This occurred although the CL_R-HPS during method IIB was invariably shorter than with method I. In the other two patients (nos. 8 and 12), VAb was noted only during method IIB at comparable H1H2, which did not produce VAb with method I (fig. 6), although the CL_R-HPS during the latter was longer. In seven patients (nos. 1–5, 9 and 10) an H1H2' CL equal to the CL_R-HPS of method IIB was scanned using the method III.
(table 1). As expected, compared with method III, the RRP-HPS with method IIB showed even a greater degree of prolongation at most CLs tested (figs. 5A–F).

When the atrial CL was altered before A₂, such that the CL_p was shorter than CL_R (figs. 5 and 6), three events were consistently noted: (1) The H₁H₂, CL preceded A₂ was shorter than if A₂ was coupled to a series of constant CLs, i.e., CL_p = CL_R. (2) The magnitude of change from CL_p-HPS to CL_R-HPS was proportional to the degree of change from CL_p to CL_R. (3) Despite the shorter CL_p-HPS with method IIB, the RRP-HPS was invariably longer than the RRP-HPS during method I, and the appearance of VAb therefore generally occurred at longer A₂, and H₁H₂ intervals than during method I or III. The VAb at times could not be demonstrated at constant atrial CLs (methods I and III) with a short CL_R, but was achieved at a comparable CL_p or shorter CL_p-HPS using method IIB.

**Effect of Varying CL_p at the Same CL_R**

At the same CL_R, two or more values for CL_p shorter than CL_R were available in seven patients (nos. 1–3, 5, 7, 9 and 11, table 1). The difference between the CL_p and CL_R in these cases was 100–300 msec. When the RRP-HPS with method IIB exceeded the RRP-HPS of method I at a minimum CL_p → CL_R difference, an increment in the CL_p → CL_R difference generally resulted in a further increase of 5–35 msec in the RRP-HPS. This occurred despite a shorter CL_R-HPS with a maximal CL_p → CL_R difference. However, for a given
CLR, we could not predict the relative increase in RRP-HPS for any CLp → CLr difference.

At the same CLR, two CLp values longer than the CLR were available in only three patients (nos. 3, 5 and 8). Insufficient data were therefore available to draw conclusions about the effect of varying CLp at the same CLR on VAb when the CLp is longer than the CLR.

Discussion

The VAb in relation to CL was originally described by Lewis\(^1\) and was attributed by Scherf\(^2\) to the effect of CL on refractory period. More recently, electrophysiologic studies by Moe et al.\(^3\) in the canine heart and by Wit et al.\(^4\) in the human heart have shown that VAb in relation to early premature supraventricular beats is due to conduction delay in the HPS and is a functional property of the normal conduction system.\(^5, 7\) It is now universally accepted that the onset of VAb or RRP-HPS is CL-dependent, varying directly with CL.\(^9-13\)

These studies are consistent with the observation of VAb during atrial fibrillation, where the sequence of long followed by short CL can occur frequently. Since the report by Gouaux and Ashman,\(^1\) it has become accepted clinical practice to distinguish VAb from ventricular beats by such CL changes.\(^4\) Therefore, while general clinical observation during atrial fibrillation and electrophysiologic studies has described the phenomenon of VAb as it relates to long CLs followed by short coupling intervals, the effect on VAb of variations in the interval preceding the long CL has not been described.

In this report, the effect on VAb of the CLp of the long-short CL sequence was systematically studied. The results indicate that the RRP-HPS is appreciably altered by CLR such that the RRP-HPS may shorten or the functional BBB may be abolished when the long CL is preceded by an even longer CL. Conversely, a functional BBB may first become manifest and/or
RRP-HPS lengthened if the long CL is preceded by relatively shorter CL. Moreover, the findings show that the dictum that RRP-HPS varies directly with CL must be reevaluated. While this characteristic of the HPS is true when CL$_p$ is constant, it is not what occurs in most patients when CL$_p$ is changing. In such instances, the RRP-HPS generally varies inversely with CL$_p$, i.e., the RRP-HPS of a given CL will be longer if preceded by a shorter CL and shorter if preceded by a longer CL.

A possible explanation for these findings may again relate to the effect of varying CL$_p$ on CL$_{app}$, as shown in figure 7. In all panels, the CL$_p$ is 700 msec. In panel A, where CL$_p$ is also 700 msec, the CL$_{app}$-HPS is 700 msec. However, when CL$_p$ is varied such that it is 900 msec (B), the CL$_{app}$-HPS is longer (720 msec) and when CL$_p$ is 500 msec (C), the CL$_{app}$-HPS is shorter (650 msec) than the corresponding atrial CL$_p$. Therefore, compared with panel A, one would expect the RRP-HPS in panel B to be longer and RRP-HPS in panel C to be shorter. However, the increase in CL$_{app}$-HPS in panel B is the result of a shortening in HPS CL from 900 to 720 msec and the decrease in CL$_{app}$-HPS in panel C is the result of a lengthening in HPS CL from 500 to 650 msec. Thus direction of change in the HPS CL significantly alters the findings expected from considering absolute HPS CL alone.

In addition, the shorter CL$_p$ lengthened the RRP-HPS more than longer CL$_p$ shortened RRP HPS, although the shorter CL$_p$ shortened the CL$_{app}$-HPS more than longer CL$_p$ lengthened CL$_{app}$-HPS. This may indicate that the HPS is also sensitive to rate of change in CL. Again, using the schema in figure 7, where CL$_p$ is 900 msec and CL$_{app}$-HPS is 720 msec, the percent shortening for the HPS CL is 180/900, or ~20%, and where CL$_p$ is 500 msec and CL$_{app}$-HPS is 650 msec, the percent lengthening for HPS CL is 150/500, or 30%. For the same variance in CL$_p$, relative to CL$_{app}$, the percent lengthening will be greater than the percent shortening, and therefore, if the HPS is sensitive to
rate of change in CL, changes of short to long CL will have a greater effect on RRP-HPS than equal changes of long to short CL.

This explanation only provides some insight into the directional changes regarding the onset of VAb with a given alteration in CLp relative to CLr: the present results do not explain the mechanism of the observed phenomena. The adjustment in refractory period of the HPS to a change in CL, although it starts immediately, takes several CLs to stabilize. The number of beats required to achieve this new steady state seems to vary considerably in different species. It is tempting to postulate, therefore, that the refractoriness of the HPS in man may also be a dynamic phenomenon that is continuously influenced by absolute duration, rate and direction of change of several preceding CLs. A sudden change in the CL may produce an overadjustment in the duration of RRP-HPS in the direction dictated by the preceding sequence of events. This could explain why the RRP-HPS values with CLp-HPS shorter than CLr-HPS sequence may exceed those expected from a CLr-HPS of constant duration. Similarly, a CLp-HPS longer than the CLr-HPS sequence may produce RRP-HPS values shorter than the CLr-HPS of a constant CL.

A fatigue effect after short CLs (i.e., a CLp shorter than a CLr) and faster recovery after CLp longer than CLr may have produced time-dependent changes in the RRP-HPS. This mechanism would not explain the present results because in several of these cases, relatively short CLs (400-500 msec) were also scanned with method I (table 1), and yet, the RRP-HPS was always shorter compared with that during longer CLs. In fact, in patients 1 and 10 (table 1), the RRP-HPS was not encountered despite achievement of H1H2 values measuring significantly less than longer CL where VAb was clearly noted. Whether similar or other mechanisms are operative cannot be determined from this study.

Although an exact model of atrial fibrillation requires an extremely complex stimulation protocol, this study has shown the pronounced effect on the functional behavior of the HPS of the CL before the long-short sequence usually described. Such effects include significant changes in RRP-HPS such that VAb may occur at longer or shorter coupling intervals than expected when CLp is not considered. In a setting of atrial fibrillation where the long CL could be preceded by considerably longer or shorter CLs, this could lead to the misdiagnosis of VAb as beats of ventricular origin. The coupling intervals (RR) of short CL at the onset of VAb could vary markedly during atrial fibrillation due
to the wide range of $CL_p$ values that may be recorded in these settings. During this study, the range of long and short CLs was limited by spontaneous sinus CLs and pacing-induced onset of AV nodal Wenckebach phenomenon, respectively.

This simplified model demonstrates that the absolute CL preceding premature supraventricular beats is not always the only determinant of VAb, but that the direction and rate of change in CLs preceding the long-short CL sequence both determine VAb in the human heart.

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