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 II1) 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 H1H1 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 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 and right atrium 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 antegrade 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 (CLp) the long CL has not been determined. We studied the effects on the functional properties of the HPS of varying CLp. 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.4 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...
with method II (fig. 1), in which, after a series of constant atrial CLs, the last A1A1 (i.e., immediately preceding the A1) was altered. The data presented here include analysis of the effect of aberrant conduction of both the last and next-to-last A1A1 cycles; therefore, the two are designated differently to avoid confusion. The last A1A1 cycle during both methods I and II is designated as the reference CL (CLR); all CLs preceding the CLR are designated as CLp. In method IIA, the CLp > CLR; whereas in method IIB, the CLp < CLR. In method I, CLR = CLr.

Definition of Terms

A1, H1, V1 — the atrial, His, and ventricular depolarizations during all constant atrial CLs.

A1', H1', V1' — the atrial, His, and ventricular depolarizations of the altered CL just before A1 during method II.

A2, H2, V2 — the atrial, His, and ventricular depolarizations resulting from coupled premature atrial stimulation.

Functional refractory period (FRP) of the atioventricular (AV) node — the shortest H1H2 interval in response to any A1A1.

RRP of the HPS — the longest H1H2 interval at which H1 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 VA with either premature atrial stimulation (A1) at atrial paced CLs slightly shorter than sinus CL or with A1 coupled to sinus beats. Patients were in sinus rhythm and had normal AH and HV intervals and were not taking any cardioactive medication at the time of study. The electrophysiologic data are listed in table 1. During VA, 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: \( CL_p = CL_R \)

METHOD II A: \( CL_p > CL_R \)

METHOD II B: \( CL_p < CL_R \)

Figure 1. Stimulation protocols. The main difference between methods I and II is that in method I the A1 is preceded by a series of constant atrial CLs, whereas in method II the CL just before A1 is abruptly altered (A1A1') compared with the preceding CLs (A1A1). In all methods, the reference CL (CLR) is the atrial CL to which A1 is coupled, whereas the CLs preceding the CLR are designated as CLp. In method IIA, the CLp > CLR, whereas in method IIB, the CLp < CLR. In method I, CLR = CLr.

Figure 2. Derivation of the corresponding His-Purkinje system (HPS) cycle length (CL) during altered CLp of method II. The schema outlines the last two atrial CLs before the A1. The atrial CLs are labeled CLp and CLr, whereas the corresponding CLp and CLR are designated as CLp-HPS and CLr-HPS, respectively. The altered CLp and CLr-HPS during method II are depicted as A1A1' and H1H2', to distinguish these from other constant CLs. Because A1H1 is constant, the CLr = CLr-HPS in method I. However, with method IIA, the CLr-HPS is greater than the corresponding CLp by the amount that A1A1' is longer than A1H1. Similarly, during method IIB the CLp-HPS is shorter than CLr by the amount that A1A1' is shorter than A1H1.
The pertinent data for each CL are provided in table 1.

The range in which CL 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, CL was 100–200 msec longer than CL or 100–300 msec shorter than CL.

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

The greater change in CL-HPS at shorter CL was attributed to a greater effect on AV nodal conduction at a shorter paced atrial CL.

**Effect of a CL Longer Than CL on VAB (table 1)**

The effect of method IIA, with which the CL was longer than the CL, could be compared in 11 of 12 patients (nos. 1–11) with method I (table 1). At the same atrial CL, 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 CL-HPS during method IIA exceeded the atrial CL of method I by 5–30 msec despite the same atrial CL. Method III was therefore used to approximate the HH' CL of method II to detect small changes in the RRP-HPS that might have been caused by subtle variation in the HH CL between the CL of methods I and II. In patients 5 and 11, the CL-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 CL-HPS of method IIA was compared with CL-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 CL-HPS sequences of 700/500, 800/600, 800/600, 600/500, 600/500, 800/600 and 650/500, where the RRP-HPS shortened to less than the FRP of.
## Table 1. Electrophysiologic Data

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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\_p = atrial preceding cycle (A\_1A\_1); CLR = atrial reference cycle (A\_1A\_1\_1); CLR-HPS = reference cycle length His-Purkinje system (H\_1H\_1 or H\_1H\_1\_1); RRP-HPS = relative refractory period of the HPS.

Intervals could not be achieved and were limited by the AV nodal FRP (figs. 4E and F).

### Effect of a CLR Shorter Than CL\_p on VAb (table 1)

The influence of method IIB, with which the CL\_p was shorter than the CLR, was compared with method I in all patients at one or more basic CLs (table 1). At the same CLR 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\_p-HPS during method IIB was invariably shorter than with method I. In the other two patients (nos. 8 and 12), VAb was not limited during method IIB at comparable H\_1H\_2, which did not produce VAb with method I (fig. 6), although the CL\_p-HPS during the latter was longer. In seven patients (nos. 1–5, 9 and 10) an H\_1H\_2' CL equal to the CL\_p-HPS of method IIB was scanned using the method III.
Figure 4. Effect of method IIA on aberrant ventricular conduction. These tracings, taken from patient 1, show the relative refractory period of the His-Purkinje system (RRP-HPS) during methods I, II A and III. (A) With method I, complete right bundle branch block (RBBB) is noted at an H, H, interval of 390 msec. (B and C) A change of CLp → CLr from 700–600 (method II) shortens the RRP-HPS such that only an incomplete RBBB occurs at an H, H, of 370 msec. The H, H, CLs in panels B and C were 610 msec. The latter CL is also scanned with method III (panel D) and shows that the RRP-HPS is even longer (400 msec) compared with method IIA (panel C). (E) A change of CLp → CLr from 700 to 500 msec. The RRP-HPS results in a decrease of this variable. The H, H, CL is 510 msec. (F) This CL is scanned with method III and again shows that RRP-HPS is longer than with method IIA (E). I and V1 = surface ECG leads; HRA = high right atrial electrogram; HBE = His bundle electrogram; T = time lines.

(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 CLp was shorter than CLr (figs. 5 and 6), three events were consistently noted: (1) The H, H, CL preceding A2 was shorter than if the A1 was coupled to a series of constant CLs, i.e., CLp = CLr. (2) The magnitude of change from CLp-HPS to CLr-HPS was proportional to the degree of change from CLp to CLr. (3) Despite the shorter CLr-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 A1, A2, and H, H, 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 CLr, but was achieved at a comparable CLr or shorter CLr-HPS using method IIB.

Effect of Varying CLp at the Same CLr

At the same CLr, two or more values for CLp shorter than CLr were available in seven patients (nos. 1–3, 5, 7, 9 and 11, table 1). The difference between the CLp and CLr in these cases was 100–300 msec. When the RRP-HPS with method IIB exceeded the RRP-HPS of method I at a minimum CLp → CLr difference, an increment in the CLp → CLr difference generally resulted in a further increase of 5–35 msec in the RRP-HPS. This occurred despite a shorter CLr-HPS with a maximal CLp → CLr difference. However, for a given
CLp, 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 Lewis1 and was attributed by Scherf2 to the effect of CL on refractory period. More recently, electrophysiologic studies by Moe et al.5 in the canine heart and by Wit et al.7 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,3 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 CLp 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

![Figure 5](http://circ.ahajournals.org/)

**Figure 5.** Effect of method IIB on aberrant ventricular conduction (VAb). Tracings are from the same patient as in figure 4. The onset of VAb (right bundle branch block) at an H4H2 of 430 msec during method IIB with a change of CLp → CLr from 400 → 600 msec. At the same CLp-HPS as panel A (i.e., 580 msec), scanning with method III reveals the onset of VAb at an H4H2 of 380 msec, which is 50 msec shorter than in panel A. Similarly, when the CLp → CLr change is from 400 → 700 msec (D), the onset of VAb occurs at a much longer H4H2 compared with method III (E and F).
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\textsubscript{p} is constant, it is not what occurs in most patients when CL\textsubscript{p} is changing. In such instances, the RRP-HPS generally varies inversely with CL\textsubscript{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\textsubscript{p} on CL\textsubscript{HPS}, as shown in figure 7. In all panels, the CL\textsubscript{H} is 700 msec. In panel A, where CL\textsubscript{p} is also 700 msec, the CL\textsubscript{H}-HPS is 700 msec. However, when CL\textsubscript{p} is varied such that it is 900 msec (B), the CL\textsubscript{H}-HPS is longer (720 msec) and when CL\textsubscript{p} is 500 msec (C), the CL\textsubscript{H}-HPS is shorter (650 msec) than the corresponding atrial CL\textsubscript{H}. 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\textsubscript{H}-HPS in panel B is the result of a shortening in HPS CL from 900 to 720 msec and the decrease in CL\textsubscript{H}-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\textsubscript{p} lengthened the RRP-HPS more than longer CL\textsubscript{p} shortened RRP HPS, although the shorter CL\textsubscript{p} shortened the CL\textsubscript{H}-HPS more than longer CL\textsubscript{p} lengthened CL\textsubscript{H}-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\textsubscript{p} is 900 msec and CL\textsubscript{H}-HPS is 720 msec, the percent shortening for the HPS CL is 180/900, or \(-20\)% and where CL\textsubscript{p} is 500 msec and CL\textsubscript{H}-HPS is 650 msec, the percent lengthening for HPS CL is 150/500, or 30%. For the same variance in CL\textsubscript{p}, relative to CL\textsubscript{H}, the percent lengthening will be greater than the percent shortening, and therefore, if the HPS is sensitive to
A fatigue effect after short CLs (i.e., a CLp shorter than a CLq) and faster recovery after CLp longer than CLq 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 H₂ 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 CL, 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
to the wide range of CLp 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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