The Characteristics of Modulated Parasystole Under Conditions of Constant and Variable Heart Rate: A Mathematical Model

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Modulated Parasystole. **A mathematical model of modulated parasystole was used to study the characteristics of entrainment of a ventricular ectopic pacemaker by ventricular activations of sinus nodal origin under conditions of constant and variable heart rate. To mimic physiological fluctuations in heart rate due to sympathetic and parasympathetic influences, the sinus nodal cycle length was modulated by three sinusoidal waves of different frequencies simultaneously (0.025, 0.1, and 0.25 Hz). To simulate the electrotonic influence of ventricular activity on the cycling of the parasystolic pacemaker, the pacemaker was modulated according to biphasic phase-response relationships characterized by an early delay phase and a late acceleration phase. A wide range of intrinsic sinus nodal cycle length to ectopic pacemaker cycle length ratios was examined. Each simulation run consisted of the computation of 1,000 pacemaker firings. Entrainment (periodic firing, sometimes combined with a periodic manifest arrhythmia) was classified into four categories: simple entrainment (periodic pacemaker firing pattern accompanied by a periodic manifest arrhythmia), complex entrainment (similar, but with a periodic manifest arrhythmia covering more than one basic firing pattern), concealed entrainment (periodic firing, no periodic manifest arrhythmia), and no entrainment. The results indicate that physiologically relevant variability of heart rate can result in electrocardiographic patterns of modulated parasystole in which entrainment of the ectopic pacemaker by the sinus rhythm is not as readily apparent. With increased variability of heart rate, simple entrainment may convert into complex, complex into concealed, and concealed entrainment into patterns that show no entrainment at all. The data should aid in our understanding and ability to recognize the various electrocardiographic manifestations of modulated parasystole.** *(J Cardiovasc Electrophysiol, Vol. 2, pp. 34-44, February 1991)*

parasystole, modulated parasystole, cardiac arrhythmia, mathematical model, heart, variable heart rate

Introduction

Modulation of the activity of a parasystolic pacemaker by electrotonic influences arriving from tissues surrounding the "protected" focus is known to generate ectopic activity typical of either parasystole or reentry, as well as more complex rhythms displaying patterns characteristic of neither mechanism. This type of behavior was first predicted by the mathematical model of parasystole developed by Moe and co-workers (1977) based on the phase-dependent electrotonic modulation of pacemaker activity described by Jalife and Moe (1976; see also Antzelevitch, et al., 1980, 1982; Ferrier and Rosenthal, 1980; Moe, et al., 1980, 1981, 1982; Jalife, et al., 1982; Antzelevitch, 1983; Gilmour, et al., 1983; Gilmour and Zipes, 1983). The predictions of the computer model were later corroborated in an in vitro biological model of parasystole (Jalife and Moe, 1979) and in a

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coupled in vitro - in vivo model (Antzelevitch, et al., 1983). The general concept of modulated parasystole has now been confirmed in numerous clinical reports and studies (Furuse, et al., 1979, 1981; Nau, et al., 1982, 1983; Castellanos, et al., 1984[a], 1984[b]; Tenczer and Littman, 1986; Tenczer, et al., 1987; Robles de Medina, et al., 1989).

Pacemaker entrainment is most readily apparent when the intrinsic ectopic pacemaker cycle length (EPCL) and sinus node cycle length (SNCL) approach "simple" ratios (i.e., EPCL: SNCL = 1:1, 4:3, 5:2, 2:1 ...). Electrotonic influences exerted by ventricular activations of sinus nodal origin can either delay or accelerate the next discharge of the ventricular pacemaker, thus causing the pacemaker to beat at a rate slower or faster than its intrinsic rate. This process of phase shifting of the parasystolic pacemaker by the beats of sinus nodal origin causes the ectopic pacemaker to fire with an average operative cycle length that is some multiple of SNCL. The extent to which pacemaker activity can be entrained in this manner is in large part determined by the degree of electrotonic influence.

The characteristics of entrainment and of manifest ectopy have been studied in a variety of biological and mathematical models for the purpose of comparison of the patterns generated with those observed in clinical ECGs. In all cases, characterization of the models was performed under conditions of constant heart rate (SNCL). In that modulation of pacemaker activity is a sensitive function of the phase of the cycle at which the electrotonus arrives, normal fluctuations in heart rate due to neurohumoral modulation of sinoatrial pacemakers are likely to play a significant role in the electrocardiographic manifestation of the ectopic pacemaker. The present study was designed to test this hypothesis in a mathematical model of modulated parasystole. Preliminary results have been published elsewhere (Swenne, 1988).

Description of the Mathematical Model

The computer model has 15 parameters as listed in Table 1. The features of the model and rules governing the simulation are described below:

The model assumes a ventricular ectopic pacemaker (EP) and a sinus nodal pacemaker (SN). The firing times for SN do not represent the times of initiation of the impulses in the sinus node proper but rather the scheduled time of arrival of the beats of sinus origin at the ventricular site adjacent to the parasystolic focus.

TABLE 1
Model Parameters

Substrate	Parameter	Meaning
Sinus node	$SNCL_0$	sinus node cycle length, unmodulated
	a_l	low-frequency heart rate modulation amplitude
	a_m	mid-frequency heart rate modulation amplitude
	a_h	high-frequency heart rate modulation amplitude
	f_l	low heart rate modulating frequency
	f_m	mid heart rate modulating frequency
	f_h	high heart rate modulating frequency
Ectopic pacemaker	$EPCL_0$	unmodulated ectopic pacemaker cycle length
	E	maximal phase shift due to electrotonic modulation
	R	reversal point of phase-response curve
	T_0	first scheduled ectopic pacemaker firing
Target tissue	APD_0	action potential duration at full recovery
	c	multiplicative constant
	τ	time constant
	X	extra AV nodal refractoriness

Neurohumoral mediated sinus node cycle length variation was mimicked by modulating the SNCL with three sinusoids of given amplitude and frequency (see Fig. 1). Electrotonically mediated ectopic pacemaker modulation is mimicked by using piecewise linear phase-response curves characterized by parameters E and R (see Fig. 2).

The sinus node starts firing at time $t = 0$.

At $t = 0$, the first scheduled ectopic pacemaker firing is at $t = T_0$ = intrinsic EPCL.

When SN and EP fire simultaneously (fusion beat), SN predominates.

The ventricles remain refractory to excitation for the entire duration of the action potential, which is calculated as follows:

$$APD = APD_0 - c^* \exp(T_r/\tau)$$

where T_r represents the recovery time (i.e., diastolic interval following full repolarization of the previous action potential) (Guevara, et al., 1984).

SN and EP beats that fire during the refractory period of the ventricle are ineffective, whereas those that occur after expiration of refractoriness activate the ventricles.

After a manifest ectopic pacemaker firing (parasystolic beat), the refractory period for reexcitation of the ventricles by the next SN impulse is extended by period X, thus simulating a refractory period for atrioventricular transmission of the next SN beat due to retrograde

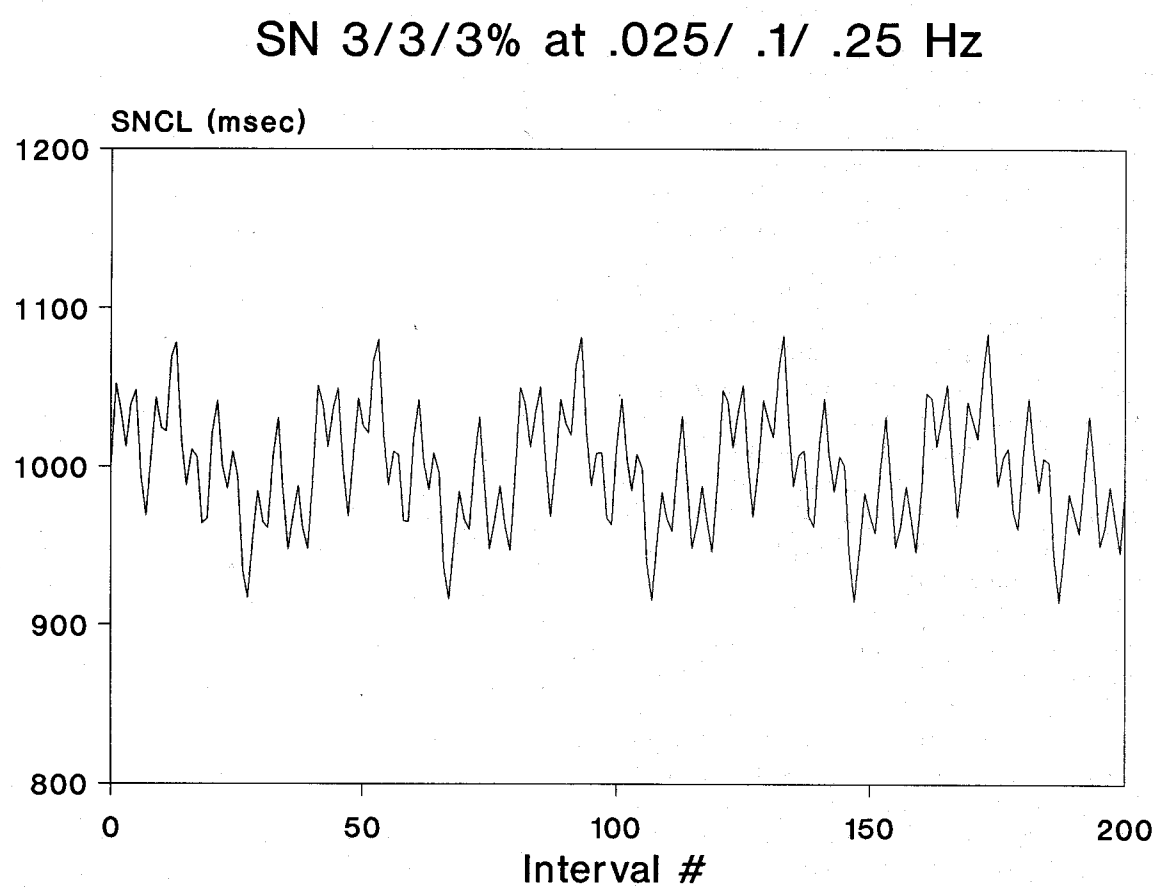

Figure 1. *An example of heart rate variability employed in the model. Modulation of the sinus node cycle length (SNCL) to ± 3% of its intrinsic value ($SNCL_0$ = 1000 msec) using a pattern which is a composite of three sinusoidal frequencies: low (0.025 Hz), medium (0.1 Hz), and high (0.25 Hz). The maximum excursion of $SNCL_0$ was 9%.*

invasion of the atrioventricular node by the parasystolic beat. This provision frequently, but not always, generates a compensatory pause after ectopic beats.

SNCL for each successive beat is calculated as follows:

$$SNCL = SNCL_0 * [1 + a_l * \sin(f_l * t) + a_m * \sin(f_m * t) + a_h * \sin(f_h * t)].$$

This equation generates a variable heart rate characterized by simultaneous modulation of the sinus rate at three different frequencies (0.025, 0.1, and 0.25 Hz; Fig. 1).

The intrinsic cycle length of the ectopic pacemaker ($EPCL_0$) determines the next scheduled EP event; this interval is electrotonically modulated according to one of the three phase-response relationships illustrated in Figure 2. The scheduled firing time of EP is shifted (delayed or accelerated) in accordance with the phase (fraction of the cycle of the ectopic pacemaker) at which the electrotonus of the SN beat arrives.

When two electrotonic events arrive within the same EP cycle, the same phase response relationship is used for both. The second event delays or advances the newly scheduled firing of EP following its modulation by the first event.

Simulations

Simulations were performed using an IBM-compatible PC computer and encompassed all of the parameter value combinations listed in Table 2. $EPCL_0$ was kept constant while the $SNCL_0$ was varied from 500–1,100 msec. Modulations of $SNCL_0$ was varied between 0% and 3% using a pattern which is a composite of three sinusoidal

frequencies (low, medium, and high; i.e., $a_l = a_m = a_h$).

Electrotonic modulation of $EPCL_0$ was according to one of three phase-response curves: maximal delay or acceleration of 10, 20, or 30% and a crossover of the relationship at 65, 55, and 45% of the EP cycle, respectively (Fig. 2; weak, moderate and strong electrotonic influence).

Each simulation run consisted of computation of 1,000 pacemaker firings and their manifestation. The model was allowed to converge to an entrainment state during the first 400 firings. The remaining 600 firings were used for periodicity analysis. Periodicity was initially assessed with a pattern length of 1 pacemaker firing (#401); if no periodicity was found, the search started again with a pattern of 2 (#401 and #402); if this was not successful, the pattern length was again incremented by one, and so on.

Firing periodicity was found when the pacemaker firing pattern repeated. The longer the pattern, the smaller the number of repetition times during firings 401-1,000: the longest pattern that could be detected in this way was one consisting of 300 firings (one repeat within the 600 firings allotted). Manifest periodicity was similarly determined. For this purpose only, manifest pacemaker firings (sinus and ectopic beats) were considered.

The results of each simulation were classified using five variables:

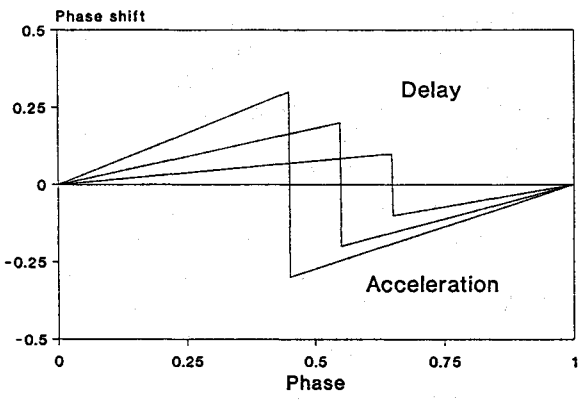

Figure 2. *Phase-response curves used in simulations. The phase is the fraction of the ectopic pacemaker cycle at which a ventricular beat of sinus nodal origin electrotonically modulates the ectopic pacemaker. Sinus nodal beats arriving early in the pacemaker cycle delay the next discharge of the pacemaker, whereas those arriving late in the cycle accelerate the next discharge.*

TABLE 2
Parameter Values Used in the Simulation

Parameter	Range	Step
$SNCL_0$	500-1,500 msec	10 msec
a_l	0-3 %	1 %
a_m	0-3 %	1 %
a_h	0-3 %	1 %
f_l	0.025 Hz	
f_m	0.1 Hz	
f_h	0.25 Hz	
$EPCL_0$	1,500 msec	
E	10-30 %	10 %
R	75-45 %	10 %
T_0	0 %	
APD_0	250 msec	
c	125	
τ	75 msec	
X	350 msec	

The amplitudes of a_l, a_m, and a_h were equal in any given run (e.g., 0/0/0%, 1/1/1%, 2/2/2%, or 3/3/3%). The parameters characterizing the phase-response curve, E and R, were also varied together, the combinations used were E = 10% and R = 75%, E = 20% and R = 65%, and E = 30% and R = 55%. The total number of simulations performed was 101 ($SNCL_0$ values) x 4 (sinus node modulation depths) x 3 (ectopic pacemaker phase-response curves) = 1,212.

N = the number of sinus node firings (manifest or concealed) in a repetitive firing pattern;
M = the number of ectopic pacemaker firings (manifest or concealed) in a repetitive firing pattern;
n = the number of manifest sinus beats in a repetitive arrhythmia pattern;
m = the number of manifest ectopic beats in a repetitive arrhythmia pattern;
k = the number of firing patterns within one manifest arrhythmia pattern.

Entrainment was categorized as follows (strong to weak):

1. Simple entrainment: the pacemaker firing pattern repeats and consists of N sinus node firings and M ectopic pacemaker firings; the manifest arrhythmia pattern is also repetitive, it repeats with each firing pattern and consists of n sinus beats and m ectopic beats (k = 1) (Fig. 3A).
2. Complex entrainment: the pacemaker firing pattern repeats, and consists of N sinus node firings and M ectopic pacemaker firings; the manifest arrhythmia pattern consisting of n sinus beats and m ectopic beats is also

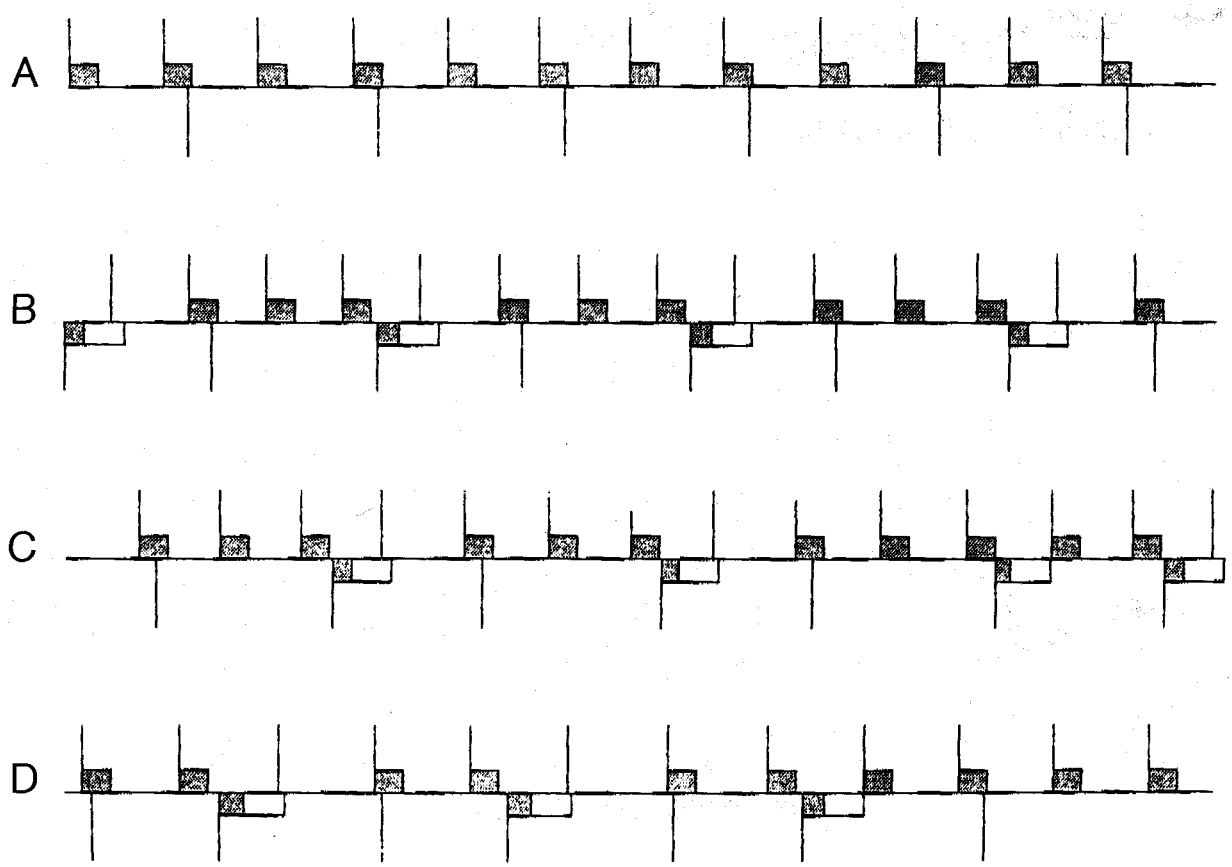

Figure 3. *Entrainment grades (from strong to weak). (A) simple entrainment; (B) complex entrainment; (C) concealed entrainment; (D) no entrainment. All tracings are symbolic electrocardiograms displaying the ventricular firing times of beats of sinus nodal origin (positive deflections and bars) as well as beats originating from a ventricular ectopic pacemaker (negative deflections and bars). The refractory periods of ventricular tissues adjacent to the ectopic pacemaker site are depicted by cross-hatched bars. The refractory period of the AV node following retrograde invasion by the ectopic impulse is represented by an open bar. Note that SN impulses blocked at the level of the AV node are diagramatically illustrated at their scheduled time of arrival in the ventricle had AV block not occurred. Panel (A) shows 2:1 firing periodicity with no manifest arrhythmia (2:0). Panel (B) shows 2:1 firing periodicity with a manifest 3:1 arrhythmia ("classical" concealed bigeminy). Panel (C) shows 2:1 firing periodicity with no manifest entrainment. The rule of bigeminy (number of intervening sinus beats between ectopic beats = n-1) does not apply here because of the interpolated ectopic beat at the end of the tracing. Panel (D) shows neither firing periodicity nor manifest periodicity.*

repetitive, but repeats after each k firing patterns ($k > 1$) (Fig. 3B).

3. Concealed entrainment: the pacemaker firing pattern repeats, and consists of N sinus node firings and M ectopic pacemaker firings; the manifest arrhythmia has no periodic pattern (n, m, and k cannot be determined) (Fig. 3C).
4. No entrainment: neither the firing pattern nor the manifest arrhythmia are periodic (neither N, M, n, m, nor k can be determined) (Fig. 3D).

Results

Figure 4 illustrates the results of a simulation in which modulation of $SNCL_0$ was 0% and modulation of $EPCL_0$ was weak (10%). The operative SNCL/EPCL ratio and incidence of ectopic beats are plotted as a function of the intrinsic SNCL/EPCL ratio (intrinsic EPCL = 1,500 msec). The plots show that either simple or complex entrainment occurred at most intrinsic SNCL/EPCL values. Entrainment was most obvious at intrinsic SNCL/EPCL values in the

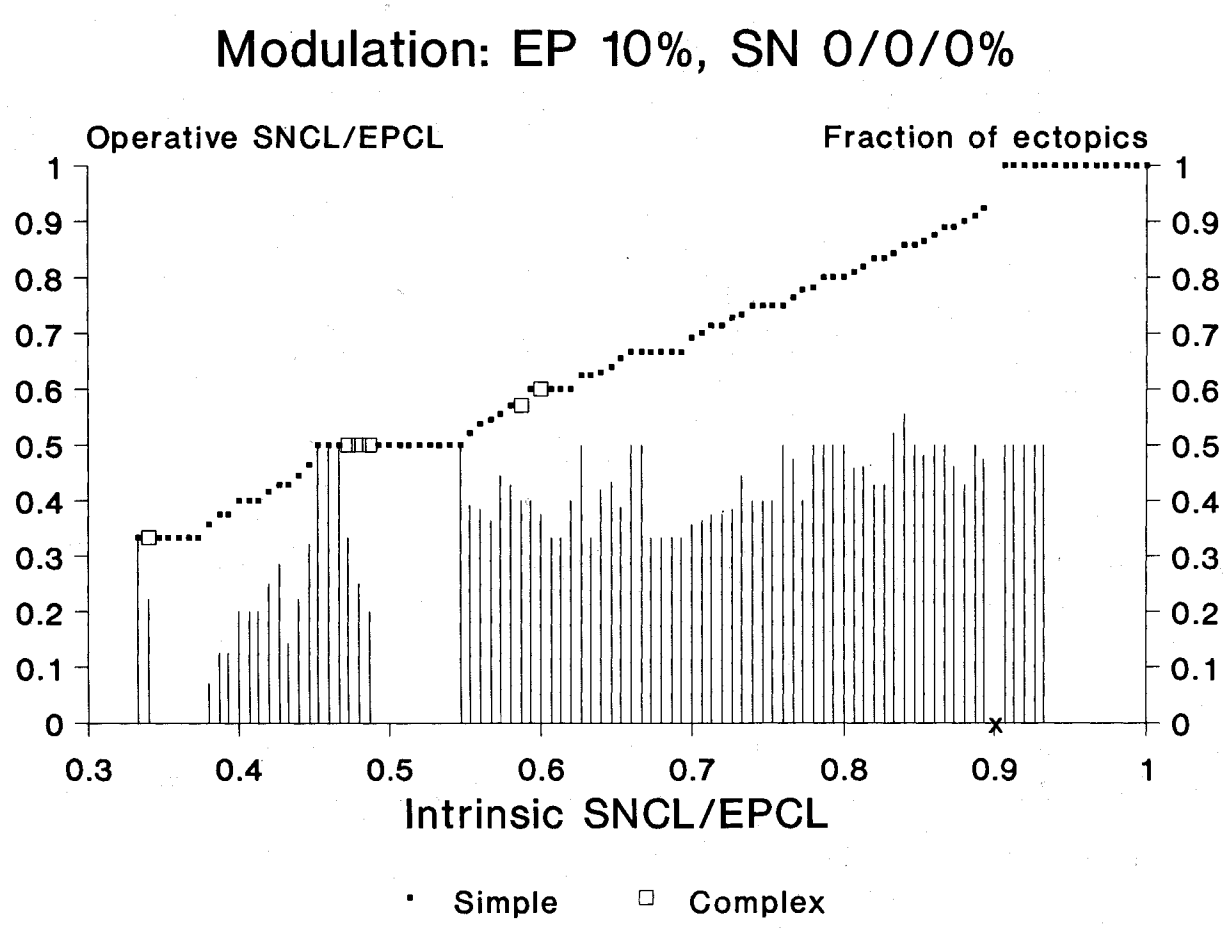

Figure 4. *Pacemaker entrainment and ectopic manifestation in simulations in which the maximal electrotonic modulation of the ectopic pacemaker was 10% and in which there was no modulation of the sinus node cycle length. The ratio of the sinus node cycle length (SNCL) to the ectopic pacemaker cycle length (EPCL) during electrotonic modulation of EP (operative) is plotted as a function of the ratio of cycle lengths in the absence of modulation (intrinsic). Only simple and complex entrainment was observed. Simulation results start at the intrinsic SNCL/EPCL ($SNCL_0/EPCL_0$ value of 500 msec/1,500 msec = 0.333. Lack of entrainment was found only at an $SNCL_0/EPCL_0$ value of 0.9. The incidence of ectopic beats as a fraction of total beats is depicted by the vertical bars. The absence of a bar indicates that there was no manifest ectopy. In this and subsequent figures, the presence of an* x *at $SNCL_0/EPCL_0$ values at which there is concealed entrainment or no entrainment indicates that the fraction of ectopic beats could not be determined because of the lack of manifest periodicity.*

neighborhood of 0.5 and 1.0; the operative SNCL/EPCL values stabilized at fixed values of 0.5 and 1. With stronger modulation of $EPCL_0$ (30%), the ranges of intrinsic SNCL/EPCL values giving rise to operative values of 0.5 and 1 were dramatically extended (Fig. 5).

When a small degree of modulation was added to $SNCL_0$ (1% at 0.025, 0.1, and 0.25 Hz), entrainment was lost at many intrinsic SNCL/EPCL values (c.f., Figs. 4 and 6) and concealed entrainment was much more commonly observed.

Similar changes were observed in the case of strong electrotonic modulation (30%; c.f., Figs. 5 and 7). Simple and complex entrainment gave way to either no or concealed entrainment.

Figure 8 summarizes the entrainment patterns encountered with increasing levels of modulation of SNCL and with a moderate level of electrotonic modulation (E = 20%) of the parasystolic focus. The greater the variability of sinus rhythm, the broader the ranges at which concealed entrainment or no entrainment are expected to occur.

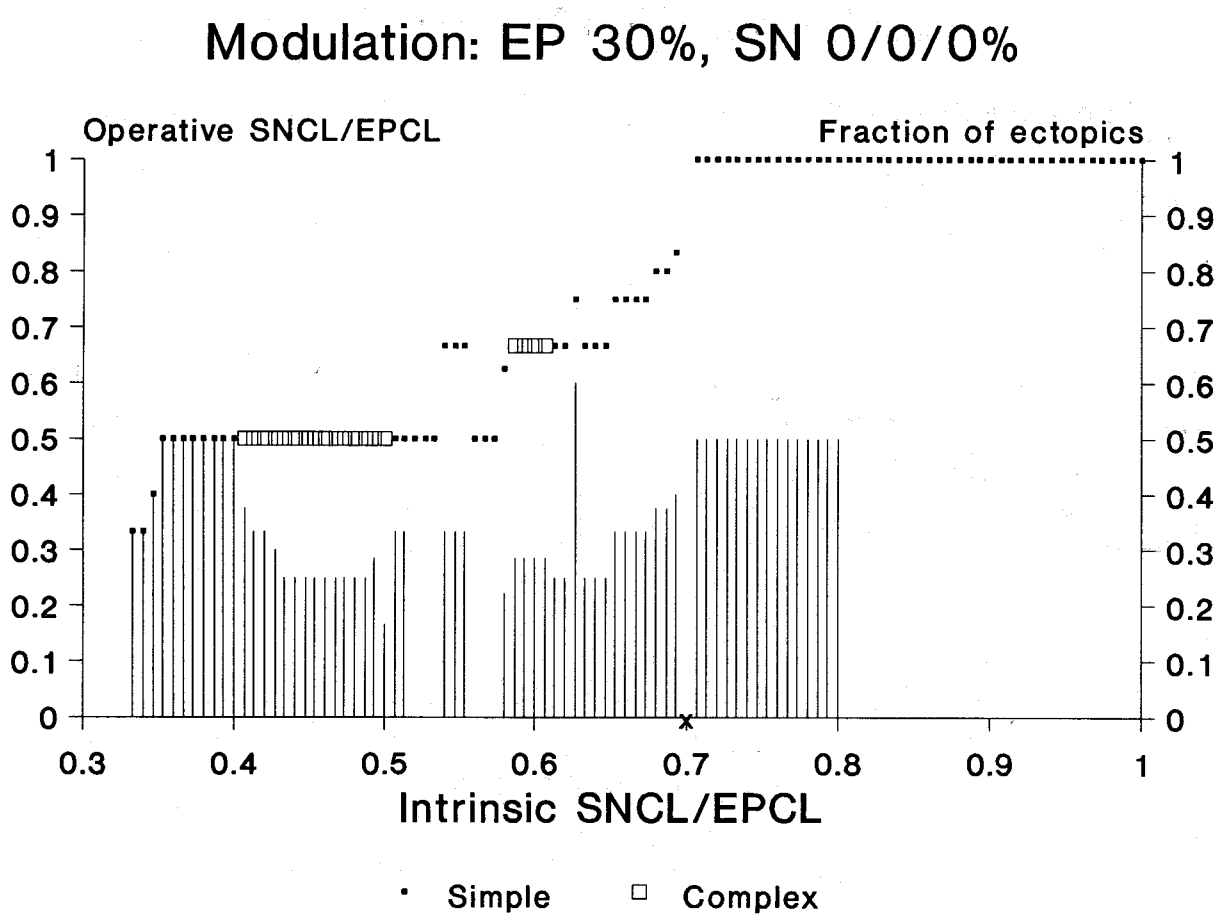

Figure 5. *Entrainment at 30% maximal electrotonic ectopic pacemaker modulation without sinus node cycle length modulation. Lack of entrainment was apparent only at a $SNCL_0/EPCL_0$ ratio of 0.7; the fraction of ectopic beats could not be determined.*

Discussion

A growing number of clinical studies are attempting to characterize premature beat manifestation in terms of a modulated parasystolic mechanism. Evidence in support of modulated parasystole as an underlyng mechanism may derive from several types of observations; chief among these are:

1. Demonstration of the existence of a phase-response curve through an inverse solution. Delineation of a phase-response relationship is achieved by analyzing ECG records in which ectopic premature beats are separated by up to three beats of sinus origin, presenting in the ECG as bigeminal, trigeminal, and quadrigeminal groupings. This is the most direct evidence for electrotonic modulation of the ectopic pacemaker. The accuracy of the inverse solution is most dependable when the intrinsic cycle length of the parasystolic pacemaker is known - appearance of two ectopic beats in sequence (Moe, et al., 1977).
2. Presence of ranges of SNCL at which stable patterns of ectopy are manifest. This is evidence for entrainment resulting from electrotonic modulation of the ectopic pacemaker.

Both lines of evidence may be difficult to obtain under some conditions. For example, when EP beats are always separated by several SN beats (no bigeminal groupings manifest), reconstruction of an accurate phase-response curve may be difficult if not impossible; multiple

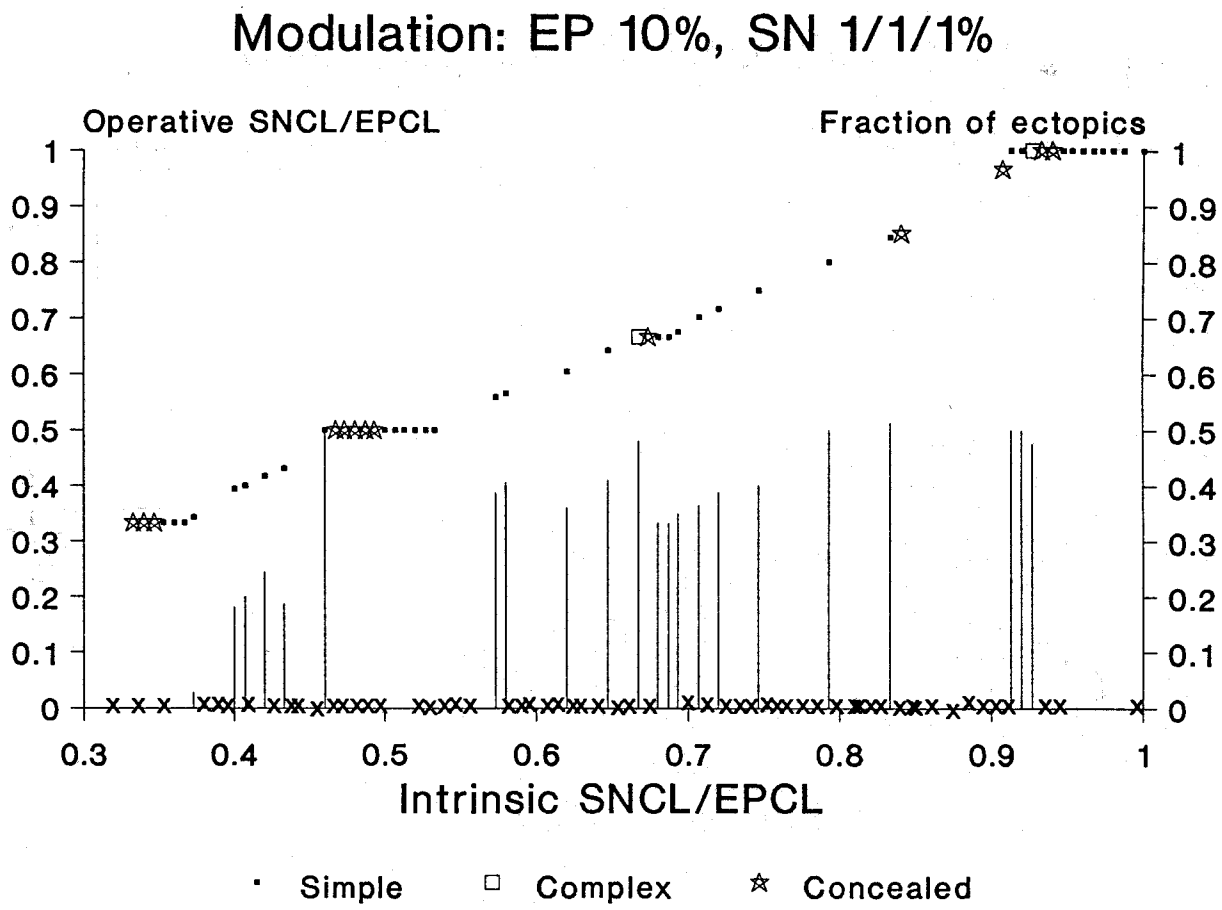

Figure 6. *Entrainment at 10% maximal electrotonic modulation of the ectopic pacemaker cycle length and 1% modulation of the sinus node cycle length at 0.025, 0.1, and 0.25 Hz.*

modulations of the ectopic pacemaker together with concealed firings greatly increase the inaccuracy of the inverse solution. Moreover, as demonstrated by this study, entrainment can be easily lost or become concealed when a relatively small amount of heart rate variability is introduced.

The maximum deviations of SNCL from $SNCL_0$ in the various simulations described in our study were 0, 3, 6, or 9% since the low, medium, and high frequency heart rate modulations are additive (see maxima and minima in Fig. 1). Such heart rate excursions are common in subjects with normal heart rate regulatory mechanisms (O'Brien, et al., 1986), although the formula employed to simulate heart rate variability provides only a first-order approximation of clinically observed variability. Typically, heart rate variability in humans shows broad peaks at three frequency ranges rather than peaks at three discrete frequencies as used in this simulation (Pomeranz, et al., 1985).

The introduction of heart rate variability as small as 1/1/1% with weak (10%) electrotonic modulation of the ectopic pacemaker caused a loss of entrainment or a shift to concealed entrainment over approximately 60% of the scanned $SNCL_0/EPCL_0$ values (c.f., Figs. 4 and 6). A similar heart rate variability under conditions of strong (30%) modulation of EP was predicted to result in loss or concealment of entrainment over nearly 40% of the scanned $SNCL_0/EPCL_0$ values (c.f., Figs. 5 and 7). With progressive augmentation of heart rate variability, simple entrainment is transformed into complex entrainment, complex entrainment into concealed entrainment, and concealed entrainment into total loss of entrainment (Fig. 8).

It should be pointed out that the frequencies selected to simulate heart rate variability show a

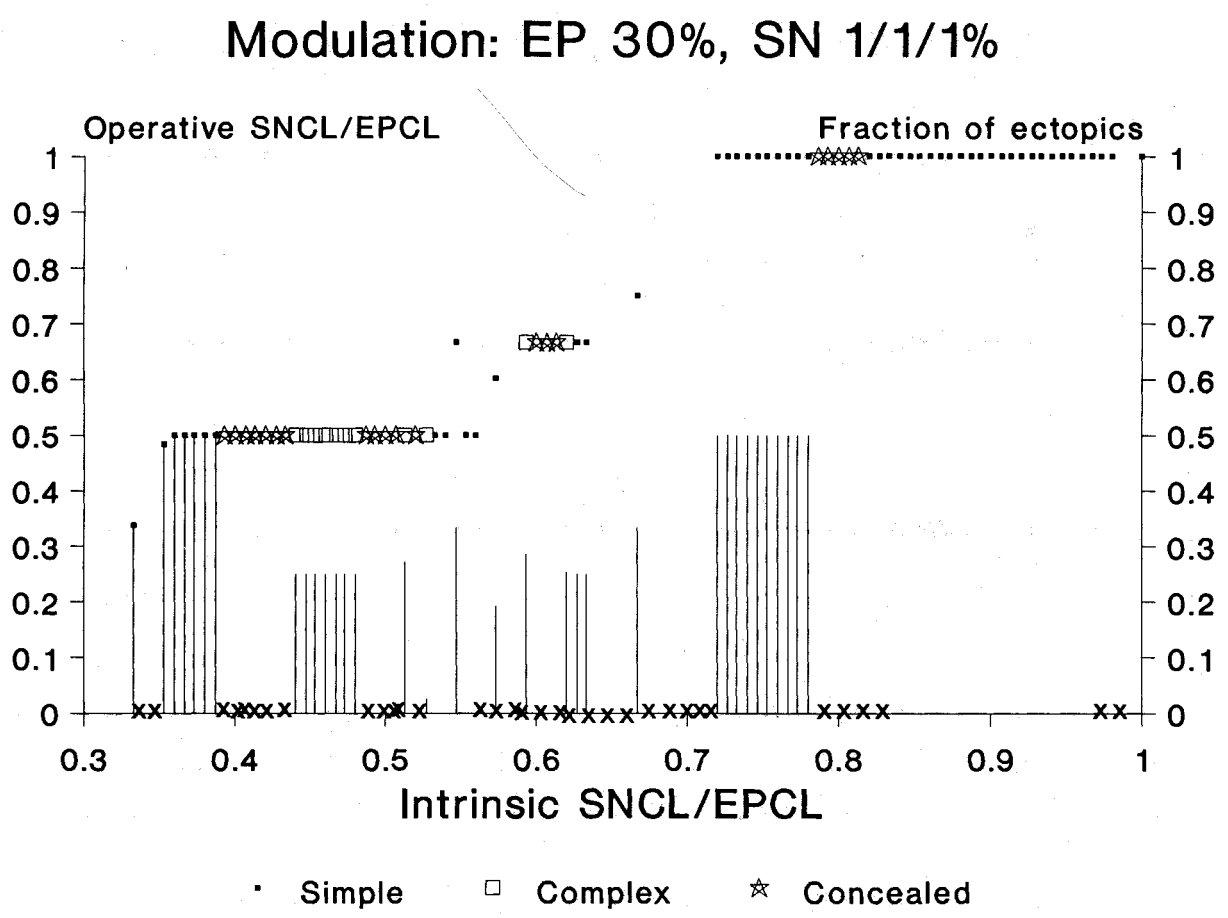

Figure 7. *Entrainment at 30% maximal electrotonic modulation of the ectopic pacemaker cycle length and 1% modulation of the sinus node cycle length modulation at 0.025, 0.1 and 0.25 Hz.*

periodicity of 40 (Fig. 1). However, this periodicity of heart rate appears to be of little consequence since simulations performed using slightly different frequencies prevented the ocurrence of such periodicity but produced qualitatively similar results in the behavior of the model.

Previous studies have not distinguished between complex and concealed entrainment; both forms are usually referred to as "concealed." Complex or concealed parasystolic rhythms are generally attributed to: 1) phase resetting or entrainment of the ectopic pacemaker such that it periodically fires during the refractory period of tissues surrounding the partially protected focus (Moe, et al., 1977); or 2) exit block, a phenomenon characterized by variable or periodic block of the ectopic pacemaker beat in its attempt to conduct out of its envelope of protection. Electrotonic modulation of the ectopic pacemaker need not be invoked in this case.

The present study suggests that heart rate variability is another important factor contributing to the appearance of patterns of complex or concealed ectopy (see also Oreto, et al., 1986). The data suggest that many cases of entrainment may be missed because the presence of heart rate variability makes their manifestation rather complex (see also Courtemanche, et al., 1989). Under these conditions, the determination of a phase-response relationship by inverse solution would be the only means to identify a modulated parasystolic mechanism. The inverse solution would also be useful in detecting triphasic phase-response relationships (Antzelevitch, et al., 1983; Åhlfeldt, et al., 1989) where the level of complexity of the entrainment process is higher even before heart rate variability is introduced.

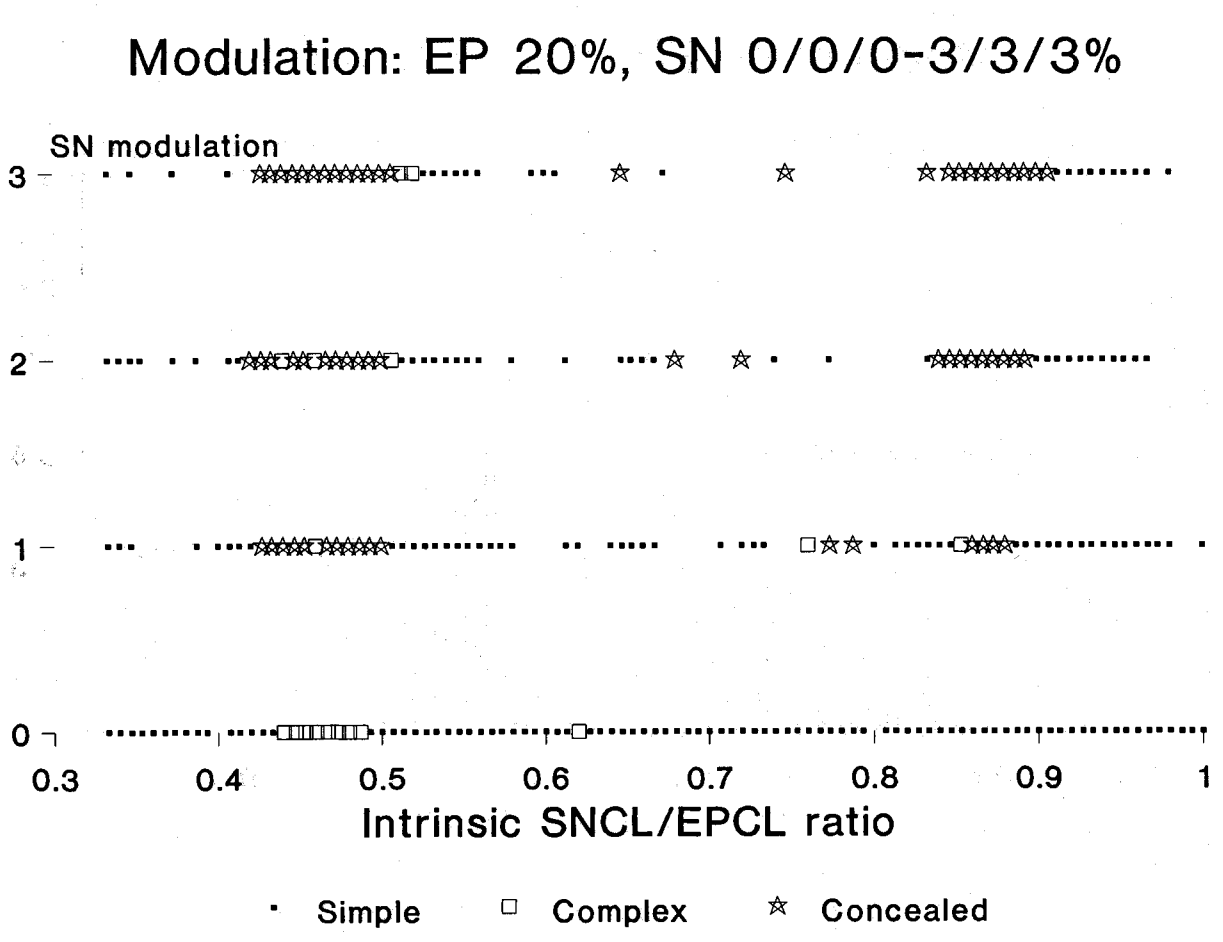

Figure 8. *The effect of heart rate variability on ectopic pacemaker entrainment. The maximum electrotonic modulation of the ectopic pacemaker cycle length was fixed at 20%, and the modulation of the sinus nodal (SN) cycle length was set at one of four levels: 0/0/0%, 1/1/1%, 2/2/2%, and 3/3/3% (0.025/ 0.1/0.25 Hz).*

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