Dynamic Interactions and Mutual Synchronization of Sinoatrial Node Pacemaker Cells

A Mathematical Model

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SUMMARY. Dynamic interactions and mutual entrainment of coupled sinoatrial pacemaker cells with different intrinsic frequencies were investigated using a computerized mathematical model. Transmembrane potentials were simulated using equations of individual membrane currents based on voltage clamp data for the sinoatrial node. The intrinsic frequency of a given cell was altered by applying bias hyperpolarizing current, or by changing the amount of slow inward current. Cells were coupled through simple ohmic resistances to form linear arrays of two or more cells. Simulations closely reproduced previous experimental work showing that the mutual interactions between pacemakers are mediated electrotonically and show phase dependence. Results from the present simulations provide an explanation for the ionic basis of these phase-dependent interactions. In addition, it is demonstrated that the mutual entrainment of coupled pacemakers can lead to their coordinated behavior (synchronization). Two pacemaker cells can synchronize at simple harmonic (i.e., 1:1, 2:1, etc.) or more complex ratios (3:2, 5:3, etc.), depending on the differences in intrinsic frequencies and the degree of electrical coupling between cells. Simulations using larger numbers of linearly connected cells yielded various patterns of pacemaker activity including 2:1 sinoatrial block and complex dysrhythmic activity. The overall results may be used to predict higher order interactions of thousands of cells comprising the sinus node. Under such a scheme, synchronization occurs not by the conducted influence of a dominant pacemaker cell, but by the mutual "democratic" interaction of individual pacemaker cells. (Circ Res 58: 706-720, 1986)

THE sinoatrial (SA) node, which serves as the normal pacemaker of the mammalian heart, is comprised of thousands of cells whose intrinsic frequencies are not identical (Bleeker et al., 1980; West and Belardinelli, 1985). The mechanism by which the electrical activities of the various SA node cells are coordinated to give rise to a single impulse once during each cardiac cycle is poorly understood.

In studies in which spherical aggregates of embryonic chick heart cells were used (DeHaan and Hirakow, 1972; Ypey et al., 1979), it was shown that, when aggregates with different spontaneous frequencies are brought into close apposition, their activities synchronize to a common frequency. Further studies (DeHaan, 1982) indicated that this behavior was related to the time-dependent formation of gap junctions between apposed aggregates. Those studies supported the contention that synchronization is mediated by electrotonic influences between clusters that require the formation of gap junctions. However, no information was provided about the electrical events and dynamic interactions that were necessary to achieve and/or maintain such synchrony. In addition, factors that determine the final cycle lengths at which pairs of electrically coupled aggregates synchronize could not be determined from those studies.

There is substantial evidence that SA node cells are electrically coupled via low-resistance pathways (Bonke, 1973; Bukauskas et al., 1977, Bleeker et al., 1980). Therefore it is possible that electrical coupling forms the basis for the coordination of automatic activity of neighboring cells. Furthermore, experimental results indicate that electrotonic currents traveling in either direction from one pacemaker cell to another can alter the duration of their respective periods (Jalife, 1984). These mutual interactions are phase dependent and can prolong or abbreviate the pacemakers' discharges so that synchronous firing can be achieved. Thus, it has been suggested (Winfree, 1980; Jalife, 1984; Delmar et al., 1986) that mutual interactions (i.e., mutual entrainment) may be the mechanism by which the spontaneous firing of individual cells or groups of cells in the SA node is coordinated to initiate the heart beat. Our experimental studies (Jalife, 1984; Delmar et al., 1986) further suggested that changes in intercellular coupling and variations of mutual entrainment patterns may be involved in arrhythmogenesis in the SA node.

In a previous publication (Michaels et al., 1984a), the equations of Yanagihara et al. (1980) were used to reconstruct the electrical activity of SA node cells. The results obtained with simulations in which brief
Methods

The electrical activity of individual sinus nodal cells was simulated with a set of differential equations of the Hodgkin and Huxley type which was devised by Yanagihara et al. (1980). Individual "cells" of this type were interconnected by means of resistive coupling. The mathematical models were programmed in FORTRAN and run on a PDP-11/73 computer (Cyberchron Corp.). Output was displayed on either a VT-125 (Digital Equipment Corp.) or a 4010 (Tektronix, Inc.) graphics display terminal during the simulations. Results of the computer runs were stored on disks and were later plotted with a Hewlett-Packard 7470A plotter.

Reconstruction of Pacemaker Activity

The use of the equations of Yanagihara et al. (1980) to reconstruct SA node electrical activity has been reported previously (Michaels et al., 1984a). Briefly, the model assumes a membrane capacitance of 1 µF/cm² in parallel with several time- and voltage-dependent membrane resistances. Membrane surface area is assumed to be 1 cm². The specific membrane currents include: (1) a “fast” sodium current (I_Na), (2) a slow inward current (I_k), (3) a potassium current (I_K), (4) a hyperpolarization-activated current (I_H), and (5) a time-dependent “leak” current (I_L). The total current (I_T) for each cell, assuming no longitudinal currents from adjacent cells, is the algebraic sum of the individual membrane currents. Membrane currents were integrated by a modified Euler method of integration (Randall, 1980). Preliminary studies indicated that a time step from 0.1 to 2 msec produced similar results. Thus, in the interests of computational speed, all of the present simulations were done at a time step of either 1 or 2 msec.

Before coupling simulations were started, it was necessary to devise a means to alter the intrinsic period (1/frequency) of individual pacemakers. One of two methods was employed: (1) application of bias hyperpolarizing (outward) current to decrease, or depolarizing (inward) current to increase, pacemaker frequencies, or (2) multiplying the maximum value of I_Na by a constant fraction (see also Joyner et al., 1983). Results with both methods are reported.

Phasic Effects of Depolarizing Current Pulses

The phase dependence of the effects of subthreshold depolarizing current pulses were determined by scanning the cycle of a single simulated pacemaker in increments of 1% of intrinsic cycle length. The changes in cycle length (phase shift, Δφ) induced by the pulse at a given phase (φ) of the cycle were summarized in phase response curves (PRC) where Δφ was plotted vs. φ, both expressed as percent of intrinsic cycle length (see Jalife and Michaels, 1985). A range of intrinsic frequencies was produced by applying bias hyperpolarizing current, or by adjusting the fraction of I_Na, and PRC were determined at each using brief current pulses of fixed magnitude (~0.2 µA/cm², 50 msec duration).

Coupling of Individual Pacemakers

To couple two or more pacemaker "cells" together (see Fig. 1), it was assumed that a coupling current (I_Coup) flows from one cell to the other that is a function of the voltage difference between the cells and the coupling resistance (R_Coup). Thus, for the case of two coupled cells of the Yanagihara type, with different intrinsic rates (one fast, F; one slow, S), the coupling current (I_Coup) can be described by:

\[ I_{Coup} = (V_F - V_S)/R_{Coup} \]

for the influence of cell S on cell F. The total current for this cell at each integration step is then the sum of the membrane ionic currents and the coupling current. Thus:

\[ I_T = (I_Na + I_K + I_H + I_L) + I_{Coup} \]

Similarly, for cell S the coupling current is described by:

\[ I_{Coup} = (V_S - V_F)/R_{Coup} \]

and the total current at each integration step for cell S is:

\[ I_T = (I_Na + I_K + I_H + I_L) + I_{Coup} \]

For each cell, I_Coup was integrated along with the other membrane currents. This method of connecting individual elements is similar to the technique used by Joyner et al. (1983) for modeling coupled cell aggregates. To eliminate the possibility that one cell would always "lead" the other, coupling currents into and out of each cell were calculated before the membrane potential of either cell was adjusted to its new value. The effects of intercellular coupling on pacemaker interaction were studied systematically over a range of coupling resistances (10 to 1 x 10⁴ kΩ).

Dynamic interactions between the F and S pacemaker rhythms are illustrated in Figure 1. The cells are coupled through an ohmic resistor as indicated schematically to the left of the traces. The intrinsic, or free-running, period of the fast (F) and slow (S) pacemakers are labeled τ_F and τ_S respectively. Control action potentials (i.e., when R_Coup = ∞) are represented by the dashed lines. When there is relatively weak coupling between cells (solid traces), firing of one cell produces subthreshold depolarizations in the other, which either accelerate or delay the next firing of that pacemaker. Depending on timing (see also Jalife, 1984). For example, in Figure 1, the second firing of cell F occurs at a phase (φ_F) near the midpoint of the intrinsic period of S and accelerates the next discharge of S by an amount known as the phase shift (Δφ_S). Similarly, this second discharge of cell S occurs at an early phase (φ_S) of cell F and produces a delaying phase shift (Δφ_F) of the next discharge of F. The phase-dependent effects of one cell on the other can be summarized in PRC where the phase shift is plotted as a function of the phase of the firing of one cell in the cycle of the other (see above).

In some simulations, the pacemakers were allowed to interact only during the time of pacemaker discharge.
During diastole, coupling resistance was set to a value where electrotonic influence was insignificant (R_{coupling} = 1 \times 10^6 \text{k}\Omega). When the membrane potential of either pacemaker exceeded a predetermined 'threshold' level, coupling resistance to the other pacemaker was reduced instantaneously to a specified value (range: 10 to 1 \times 10^6 \text{k}\Omega). This protocol allowed for only the 'phasic' influence of one pacemaker on the other.

In a final set of simulations, interactions among linear arrays of more than two (usually three to five) coupled pacemaker "cells" were studied. The intrinsic frequency of each pacemaker could be adjusted as described above, and the mutual interactions of the pacemakers were determined by varying the coupling resistances.

Results

Control of Pacemaker Periodicity

The effects of various amounts of bias hyperpolarizing current on pacemaker frequency are illustrated in Figure 2A. The traces show the reconstructed membrane potential of a single simulated pacemaker cell. In the top trace (control), when no current was applied, the intrinsic cycle length was 318 msec. Application of hyperpolarizing current at various strengths produced decreases in pacemaker frequency. When current strength exceeded 0.466 \mu A/cm^2, all spontaneous activity ceased (not shown). At all values of the bias current, both maximum diastolic potential (MDP) and action potential overshoot increased slightly. The effects of decreasing the slow inward current are shown in Figure 2B. The top trace shows control where the intrinsic period (cycle length) was again 318 msec. Lower traces show the effects of progressively reducing i_s, which again reduced pacemaker frequency. Reduction in i_s was accompanied by a decrease in MDP and action potential overshoot. Reduction of i_s below 0.5\times normal eliminated pacemaker activity (not shown).

Electrical Coupling and Mutual Entrainment

The interactions of two simulated cells (with different intrinsic periods) at various levels of coupling resistance are illustrated in Figure 3. Setting the coupling resistance (R_{coupling}) to the high value of 1 \times 10^6 \text{k}\Omega (Fig. 3, panel A) prevented any interaction between the pacemakers, and they discharged at their respective intrinsic frequencies. In panel B, R_{coupling} was decreased to 300 k\Omega. The two pacemakers continued to beat at different rates. However, they no longer discharged at their intrinsic frequencies. In fact, a 5:3 (F:S) Wenckebach-like pattern of mutual entrainment was established, with individual periods varying predictably in a manner that depended on the phasic relations between F and S. For example, the second discharge of F (panel B, top trace) occurred relatively early (\phi_S = 294 msec) within the S period (bottom trace). This discharge induced a brief subthreshold depolarization and delayed the approach to threshold for a second S discharge. This perturbation would have produced a major prolongation of the S period if it were not for the fact that the third F discharge, occurring within that same period, captured the S pacemaker and yielded an entrained period that was slightly longer than the control (cf. panel A). The fourth F action potential occurred at a \phi_S of 328 msec and captured the third S discharge, abbreviating the second S period by 180 msec from control. S discharges also produced phasic variations in F pacemaker periodicity (see periods 4 and 9 in panel B). However, these variations always were much
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Ionic Basis of Phase Delay and Phase Advance

Phasic interactions such as those demonstrated in Figures 3 and 4 have been observed in biological preparations and in computer simulations of cardiac pacemakers (Jalife and Moe, 1976; Sano et al., 1978; Jalife et al., 1980; Clay et al., 1984; Jalife and Michaels, 1985). In every case, when a brief depolarizing input perturbs the pacemaker rhythm during the first half of its intrinsic period, the subsequent discharge is delayed. A similar input occurring during the second half abbreviates the pacemaker period. These phasic changes have been plotted in phase response curves (PRC) which can be used to predict the entrainment behavior of cardiac pacemakers when interacting with periodic perturbations from their surroundings. However, except for one recent study in embryonic tissue (Clay et al., 1984), descriptions have been phenomenological, and the ionic mechanism has not been explained. We therefore examined the changes occurring in specific membrane currents when the activity of a simulated sinus node cell is perturbed by brief subthreshold depolarizing inputs scanning the spontaneous cycle. Figure 5 shows the effects of a depolarizing current pulse given at two different phases of a pacemaker period whose duration had been increased to 606 msec by the application of a bias hyperpolarizing current of 0.4 μA/cm² (not shown). In both A1 and B1, the records show (from top to bottom) the time course of membrane potential (V_m), total membrane current (I_m), slow inward current (I_S), potassium current (I_K), hyperpolarization-activated current (I_H), sodium current (I_Na), and leak current (I_L). Positive deflections are outward current; negative deflections are inward current.

As has been discussed previously (Yanagihara et al., 1980; Michaels et al., 1984a) the most important cause of phase 4 depolarization in the standard model is a time-dependent increase in I_S. This current is also responsible for the action potential upstroke. In the case of the present simulations (see panel A1 of Fig. 5), constant hyperpolarization prolongs the time course of I_S during diastole, which results in cycle length prolongation, and increases the contribution of I_Na to diastolic depolarization, particularly during the second half of the cycle. In panel A, the pulse applied 297 msec after the second discharge (i.e., \( \phi = 49\% \)) produced a brief subthreshold depolarization (see top trace). After termination of the pulse, the slope of phase 4 be-
FIGURE 3. Effect of coupling resistance on interaction of two pacemakers with different intrinsic periods. In all panels, a bias hyperpolarizing current (0.4 µA/cm²) was added to the slower cell (lower trace), whereas no changes were made to the fast cell (upper trace). Coupling resistances: panel A, 1 x 10⁶; panel B, 300; panel C, 200; panel D, 10 kΩ. In panel A, cells are uncoupled and beat at their intrinsic periods (upper = 318, lower = 606 msec). In panels B and C, complex F:S ratios of 5:3 and 5:4, respectively, occurred. In panel D, cells were mutually entrained in a 1:1 fashion to a common period of 395 msec.

came transiently negative, and there was a significant delay in the approach to threshold. Finally, the resumption of slow diastolic depolarization gave way to the third pacemaker discharge. The effect of the current pulse on total membrane current is seen in the second trace of panel A1 and at expanded scale in panel A2, which also illustrates the time course of iₛ. During the initial part of diastole, iₛ was inward and declining. As expected, upon application of the pulse, iₛ increased markedly in the inward direction. During the pulse, there was a decrease in iₛ followed by an increase, both of which reflect the changes in the individual membrane currents induced by the sudden change in membrane potential. Upon termination of the pulse, iₛ abruptly became slightly outward, then gradually decayed and became progressively more inward, until it gave rise to the third action potential.

The primary factors involved in the phase delay illustrated in Figure 5A are changes in the time course of the slow inward current and the sodium current. Note that, during the pulse, both iₛ (panel A2) and iₐ (panel A1) rapidly increased. However, after termination of the pulse, both currents underwent a gradual decline which eventually reversed. These transient decreases in iₛ and iₐ reflect changes in the balance between the voltage-dependent activation and inactivation gating variables for these currents. The other time-dependent inward current, i_H, did not seem to play a major role in these phasic changes, since it was slightly reduced by the current pulse. Both of the outward currents, i_K and i_L, were

FIGURE 4. Effects of coupling resistance on interaction of pacemakers with dissimilar intrinsic periods. In all panels, the period of the slower pacemaker was prolonged by lowering the fraction of iₛ to 0.6x normal. No changes were made to the faster (upper trace) pacemaker. Coupling resistances: panel A, 1 x 10⁶; panel B, 500; panel C, 400; panel D, 10 kΩ. Complex patterns of mutual entrainment were seen at intermediate levels of coupling, and 1:1 mutual entrainment was seen at the lowest resistance.
FIGURE 5. Membrane potential and membrane currents during phase delay and phase advance produced by a brief depolarizing current pulse (-0.2 µA/cm², 50 msec duration). Top traces of panels A1 and B1 indicate membrane potential. Dotted lines indicate control activity without current pulses. Pulse bars below action potential traces show timing of brief current pulses. An early pulse (panel A1) delays, whereas a later pulse (panel B1) advances the next spontaneous firing. Shaded traces indicate total membrane current (IT) and individual membrane currents. Boxes in IT and IS of panels A1 and B1 indicate areas shown in larger scale in panels A2 and B2. For complete description, see text. Calibrations: vertical bar to right of top traces (membrane potential) equals 85 mV. Time calibration (horizontal) at lower left equals 500 msec for panels A1 and B1, and 250 msec for panels A2 and B2. Current calibration (vertical) at lower left equals 2.5 µA/cm² for panels A1 and B1 and 0.5 µA/cm² for panels A2 and B2.

increased following the pulse, and contributed significantly to the phasic delay, since they were responsible for making IT transiently outward.

Panels B1 and B2 show results obtained when the depolarizing pulse was applied at a later phase (ϕ = 51% T intrinsic). The abbreviation of the pacemaker period observed under these conditions (top trace) is the result of net increases in IS and INa during diastole, and forced IT to become transiently outward (Fig. 5, panels A1-A2). Acceleration of the next pacemaker discharge by an appropriately timed depolarizing input was observed as a result of marked increases in IS and INa during diastole, and when IT, although reduced, was not outward at any point following that input.

F and S Intrinsic Frequencies and R촉 Determine Mutual Entrainment

Previous studies (see Jalife and Michaels, 1985) indicate that the phase-dependent effects of a perturbing stimulus on the cycle length of a pacemaker depend not only on the magnitude and duration of the stimulus and its time of occurrence during the pacemaker cycle, but also on the intrinsic cycle length of the pacemaker being perturbed. This suggested that the patterns of mutual entrainment of two coupled pacemakers might be a function of the degree of coupling between them as well as of the differences in their intrinsic frequencies. To investigate this systematically, we carried out simulations at various levels of coupling resistance, where the intrinsic period of the faster (F) pacemaker was always 318 msec and the intrinsic period of the slower (S) pacemaker was adjusted to one of four values by adding different amounts of bias hyperpolarizing current. Each run permitted the interactions for 6 seconds. The ratio of the number of firings of F to the number of firings of S was determined and plotted as a function of the log of coupling resistance. Figure 6 summarizes the results of these simulations. The intrinsic F:S firing ratios are seen in Figure 6 at the far right of the graph where coupling resistance is highest and there is no interaction between pacemakers.

When coupling resistance was lowest (Fig. 6; log R촉 = 1), there was 1:1 mutual entrainment of F reached and the pacemaker discharged. Note that there was no region of decline for IS at any time during diastole in this run. This is in sharp contrast to what was observed in the case of phase delay (panels A1 and A2). In panel B1, the pulse also produced a marked increase in IS, of about 0.21 µA/cm². This current declined slightly after the pulse and then increased gradually until the pacemaker discharged. The hyperpolarization-induced current (IH) decreased more slowly throughout the remainder of diastole. The outward currents, IK and IL, both were increased by the pulse, but not sufficiently to make IT outward. The net result was that, even though immediately after the perturbation IT was less negative than would have been expected for the control, significant increases in IS and INa led to a rapid increase in total inward current and to a faster approach to threshold. In summary, a depolarizing perturbation occurring during the first half of the pacemaker period could delay the next spontaneous discharge when it produced a transient decline in IS and INa during diastole, and forced IT to become transiently outward (Fig. 5, panels A1-A2). Acceleration of the next pacemaker discharge by an appropriately timed depolarizing input was observed as a result of marked increases in IS and INa during diastole, and when IT, although reduced, was not outward at any point following that input.
and S, regardless of the difference in their intrinsic frequencies. Furthermore, at this level, the F discharge preceded the S upstroke by a brief and fixed interval (Fig. 7). In Figure 6, as \( R_{coup} \) was increased, there was a progressive decrease in the degree of interaction between F and S. Yet, the firing ratio remained at, or very close to, 1.0 for coupling resistances that were lower than 200 k\( \Omega \). In all curves, however, there was an abrupt increase in the firing ratio at some level of coupling resistance. It is evident from Figure 6 that when the disparity between the intrinsic frequencies of the two pacemakers was greater, the abrupt change in F:S firing ratio occurred at lower levels of \( R_{coup} \) (e.g., compare curve 4 with curve 1), and the slope of the change was steeper. It is during the region of steepest positive slope that the complex patterns of pacemaker interaction are observed (see Fig. 3, B and C). Note also that as the slope of this region increased, its width diminished. Finally, as \( R_{coup} \) was further increased, the firing ratios reached values which corresponded in each case to the intrinsic F:S frequency ratios.

In summary, the pattern of mutual entrainment depended not only on the phase dependence of the influence of one pacemaker on the cycle length of the other, but also on the differences in their intrinsic periods. Furthermore, when the disparity between the frequencies of the two pacemakers increased, complex patterns of mutual interaction developed at lower levels of \( R_{coup} \). Interestingly, when the intrinsic frequencies were quite different (Fig. 6, curve 4), there was an intermediate zone of coupling resistance where the entrainment ratio (2.0) was higher than the intrinsic F:S ratio (1.91) under those circumstances. This was the result of the phase-delaying and phase-advancing effects of two subsequent F firings occurring in every S period, which entrained the latter to a constant duration of twice the length of the F period (see also first S period in Fig. 3C).

**Mean Cycle Length and Coupling Resistance**

The data from the simulations presented in the previous section have been replotted in Figure 7 to illustrate how the entrainment cycle lengths vary with changes in coupling resistance and phasic relations. In each panel, the mean cycle lengths and corresponding F-S discharge intervals are plotted against the log of \( R_{coup} \). The F (i.e., the “standard”) cell is represented by the solid squares and the S pacemaker by the solid circles. The stable F-S intervals obtained at the lower values of \( R_{coup} \) during 1:1 entrainment are shown by the open triangles. Data for four different levels of bias current (panel A, 0.1; panel B, 0.2; panel C, 0.3; panel D, 0.4 \( \mu \)A/cm\(^2\)) applied to S are presented. The intrinsic cycle lengths of F and S in each panel are observed when the coupling resistance is highest (Fig. 7, rightmost data points).

In every case, when \( R_{coup} \) is lowest, the F-S intervals are brief and the pacemakers are mutually entrained in a 1:1 manner (see also Fig. 6). As the difference between intrinsic F and S periods increases (panel A, 32 msec; panel B, 78 msec; panel C, 150 msec; panel D, 288 msec), the mean common cycle length also increases. Note that at the highest level of cell-to-cell coupling (lowest \( R_{coup} \)), the common cycle length is always closer to the intrinsic F period. Moreover, in all panels, as \( R_{coup} \) increases, F-S intervals also increase and the common cycle lengths gradually abbreviate. Finally, at a critical point of coupling resistance, 1:1 entrainment is lost; F-S intervals are no longer fixed (not shown), and the F and S cycle lengths begin to diverge as the two pacemakers interact at more complex, subhar-
monic (i.e., 3:2, 5:4, 2:1, etc.) levels of entrainment. This loss of one-to-one entrainment occurs at lower levels of $R_{\text{coup}}$ and becomes narrower as the disparity between intrinsic cycle lengths increases. The overall changes are the result of the decreasing electrotonic interactions between F and S.

**Loss of Entrainment and the Phase-Response Curve**

As indicated previously, at intermediate levels of coupling resistance (e.g., $\log R_{\text{coup}} = 2.8$ to 3.2 in Fig. 7A), once 1:1 entrainment had been lost, F and S did not become completely independent of each other, but continued to interact, regardless of their intrinsic frequencies. Indeed, as the F-S intervals changed from one beat to the next, the pacemakers phase-shifted each other’s rhythm and produced various forms of Wenckebach-like periodicity (Fig. 3), 2:1 entrainment (Fig. 7D), or more complex arrhythmic patterns. We investigated the mechanism of these phase-dependent patterns more quantitatively through the use of PRC. Figure 8 shows PRC for S (panel A, intrinsic period = 468 msec) and F (panel B, intrinsic period = 318 msec) for two levels of coupling resistance at which there were complex interactions between the pacemakers. In these computer runs, the initial phase of S was varied systematically with respect to the faster pacemaker discharge. In this manner, it was possible to scan the S period and measure the phase shifts induced by individual F discharges in the S period as a function of their timing within that period. The phase dependence of the changes induced by the S discharge in the F period were measured similarly. In panel A, the PRC show that F discharges occurring during the first half of the S period delayed, whereas those
FIGURE 8. Phase-response curves showing the influence of the discharge of one pacemaker on the cycle length of the other at two different levels of coupling resistance. In both panels, the phase shift ($\Delta \phi$) is plotted as a function of phase ($\phi$), both expressed as percent of intrinsic periods, at coupling resistances of 300 (filled squares) and 600 (filled triangles) k Ohm. Panel A shows the influence of the firing of the faster (F) pacemaker on the cycle length of the slower (S), whereas panel B shows the effects of the firing of S on the cycle length of F. At both levels of coupling, the changes induced by F in S were greater than those induced by S in F. In both instances, increasing the coupling resistance decreased the influence of one pacemaker on the cycle length of the other.

PRC "Strength" and Pacemaker "Dominance"

Analysis of the results presented in Figure 7 reveals that, regardless of the difference in F and S intrinsic cycle durations, the mean cycle length at the 1:1 entrainment level (i.e., lowest $R_{coup}$ values) is always closer to the intrinsic F period, suggesting that the overall cycle length changes that are necessary to maintain stable entrainment are larger for S than for F. In addition, comparison of panels A and B of Figure 8 indicates that the influence of pacemaker F on the cycle length of S was always greater than the other way around, regardless of the coupling resistance. Similar results were observed in simulations in which the frequency of S was slowed by reducing $I_S$ (not shown), as well as in our experimental sinus node preparations (Takayanagi and
Jalife, 1986), and also were obtained in a study of mutual entrainment with an electronic parallel conductance model (Ypey et al., 1980).

To gain insight into the mechanisms of this different sensitivity of fast and slow pacemakers to phasic perturbations, we studied the effects of brief depolarizing pulses on rhythmicity of a simulated pacemaker whose intrinsic period was prolonged systematically. Results are summarized as PRC in Figure 9. Curve A shows results when all model parameters were standard. The PRC shows marked asymmetry with a maximum phase delay of 2.83% and maximum phase advance of 14.47%, and resembles that obtained for F with weak F:S interactions in Figure 8B (triangles). In curve B of Figure 9, $i_s$ was reduced to 0.6x normal. Under these conditions, the maximum delay was increased to 6.74%, and the maximum acceleration to 23.04%, with a concomitant increase in the steepness of the negative slope region of the PRC. The curve now resembled the PRC obtained for S in Figure 8A. Curve C (Fig. 9) was obtained when a bias hyperpolarizing current of 0.4 $\mu$A/cm$^2$ was applied, which increased the intrinsic period to 606 msec. Under these conditions, the PRC increased in total amplitude with a maximum delay of 29.98% and maximum acceleration of 29.00%, and a major increase in the steepness of the negative slope region. This curve was now similar to the PRC of S obtained with stronger coupling (Fig. 8A). Hence, regardless of the method employed to slow pacemaker activity, the sensitivity of a relatively slow pacemaker to brief depolarizing perturbations is greater than that of a pacemaker whose cycle length is briefer. In the case of our simulations, both hyperpolarization and reduction of $i_s$ diminish the contribution of this current to pacemaker activity.

**Phasic vs. Tonic Interactions**

When two pacemakers are coupled through a relatively low resistance, variations in the potential difference between them actually separate the effects of one pacemaker on the other into two major components: (1) the continuous "tonic" interaction of the pacemakers (e.g., during diastole), and (2) the "phasic" influence resulting from electrotonic current flow during the discharge of an action potential (e.g., Fig. 3, B and C). Thus, the PRC obtained under a given set of conditions must reflect contributions of both components. In an attempt to separate one from the other, we performed simulations in which $R_{coup}$ was maintained at a very high value (1 x $10^6$ kΩ) for most of the computer run, and was set to a predetermined low level only during the firing of an action potential (see Methods). In this way, the phasic influences of either pacemaker on the other were maintained, while tonic effects were negligible. The results obtained under these conditions of "pulsed coupling" were qualitatively similar to those obtained when coupling was continuous. Pacemaker interaction depended on $R_{coup}$ and progressed from 1:1 synchronization through "Wenckebach-like" and more complex patterns, to total loss of synchrony as $R_{coup}$ increased. Quantitatively, there were differences between pulsed and continuous coupling. Under pulsed conditions, the mean entrained cycle lengths during 1:1 synchronization were shorter than those obtained with continuous coupling. This result was not unexpected, since, with pulsed coupling, the continuous electrotonic "pull" of the slower pacemaker on the faster during diastole was eliminated. In addition, throughout the range of 1:1 entrainment, the F:S interval was slightly longer in the case of pulsed coupling. This too would be expected from the absence of continuous pacemaker interaction. The ranges of coupling resistance where 1:1 entrainment was lost and Wenckebach-like patterns were observed had the same width as those obtained with continuous coupling (see Fig. 7), but began at lower levels of $R_{coup}$. Thus, the actual pattern of complex pacemaker interaction seen at a given value of $R_{coup}$ differed when the two different coupling methods were employed. The major conclusion of these studies, however, is that the entrainment patterns seen under conditions of continuous coupling in our model are primarily a function of the phasic influence of the electrotonic manifestation of the discharge of one pacemaker on the activity of the other.

![Figure 9. Phase-response curves (PRC) for the effects of a brief depolarizing input applied at different phases of the cycle. In all cases, a brief current pulse (~0.2 $\mu$A/cm$^2$, duration 50 msec) was used to scan the pacemaker cycle in 1% increments. The phase shift ($\Delta \phi$) was plotted as a function of phase ($\phi$), both expressed as percent of the intrinsic pacemaker period (%T). Curve A represents results with the standard model (i.e., when $r = 318$ msec). In curve B, $i_s$ had been reduced to 0.6x normal ($r = 460$ msec) and a more symmetrical PRC was obtained. For curve C, a bias hyperpolarizing current of 0.4 $\mu$A/cm$^2$ was applied ($r = 606$ msec), and an even more symmetrical PRC was obtained.](http://circres.ahajournals.org/Downloaded_from)
Can the Entrained Cycle Length be Predicted?

From the simulations presented thus far, it appears that the mean cycle length at which F and S synchronize depends on two major factors: (1) the difference in their intrinsic periods, and (2) the coupling resistance. Results presented above (Fig. 7) demonstrate that at the lowest coupling resistance ($R_{\text{coup}} = 10 \, \text{k}\Omega$) when the difference in F and S intrinsic periods increased, the mean cycle length also increased. However, in all cases, the mean cycle length was closer to the intrinsic period of F than to that of S. It is also evident that at any given set of intrinsic periods, as $R_{\text{coup}}$ was increased in the zone of 1:1 synchronization, mean entrained cycle length gradually decreased. In an attempt to provide a means for predicting the entrained cycle length, data were plotted as shown in Figure 10. The mean entrained cycle length ($T_{\text{mean}}$) is expressed as percent of the F intrinsic period ($T_F$) plotted vs. the difference between the intrinsic F and S periods ($T_S - T_F$) also expressed as percent of $T_F$. Data are shown for three different levels of coupling resistance. Arrows indicate those data obtained from simulation results reported in Figures 6 and 7. To verify the predictive value of the relationship, we performed additional simulations in which the intrinsic periods of both pacemakers were altered by the application of bias hyperpolarizing current over the entire range at which spontaneous activity was observed (see Fig. 2). When the data resulting from these simulations were normalized by expressing them as percent of $T_F$ (Fig. 10), they provided additional values for the relationship.

**Figure 10.** Predictability of mean common period of synchronized pacemakers. All data are simulations where pacemakers were mutually entrained in a 1:1 fashion. The mean period ($T_{\text{mean}}$) is plotted as a function of the difference in intrinsic F and S periods, both expressed as percent of the intrinsic period of the faster pacemaker ($T_F$). Values are plotted at three levels of coupling resistance ($R_{\text{coup}}$): 10 (open triangles), 60 (filled triangles), and 180 (filled diamonds) $\text{k}\Omega$. Arrows indicate data obtained from simulations plotted in Figures 6 and 7.

**Coupling and Mutual Entrainment of Multiple Pacemakers**

To investigate the possibility that multiple pacemakers would synchronize by means of phase-dependent mutual interactions, an additional series of simulations was done where multiple pacemakers with different intrinsic periods were coupled through ohmic resistances in a linear, one-dimensional strand. Figure 11 shows the results of three such simulations performed at three different levels of coupling resistance ($R_{\text{coup}}$). The intrinsic periods of the individual pacemakers were altered by applying various amounts of bias current. Panel A shows results obtained when the coupling resistance was set to a value high enough to prevent any interac-

**Figure 11.** Effects of coupling resistance on interactions of a linear array of multiple pacemakers. In all panels, intrinsic frequencies were altered by applying various amounts of bias hyperpolarizing current (from top to bottom: 0.6, 0.15, 0.3, 0.45, and 0.6 $\mu\text{A/cm}^2$). In panel A, coupling resistance was set to $1 \times 10^8 \, \text{k}\Omega$, and pacemakers fired at their intrinsic periods with no interactions. For panel B, coupling resistance was set to 10 $\text{k}\Omega$, and pacemakers mutually entrained to a common period of 634 msec. In panel C, raising coupling resistance to 300 $\text{k}\Omega$ resulted in a complex arrhythmic pattern of pacemaker interaction.
tions between the pacemakers. The large amount of current applied to the top and bottom pacemakers prevented any spontaneous discharges. In the absence of interaction, the intrinsic periods of the second, third, and fourth pacemakers were 371, 469, and 773 msec, respectively. In panel B, when $R_{\text{coupl}}$ was set to a low value, all cells were synchronized to a common period of 634 msec. When coupling resistance was increased (panel C), a complex pattern of interaction developed. Under these conditions, the second and third pacemakers were mutually entrained in a 1:1 pattern with varying cycle lengths and coupling intervals. The ratio of firing of the third and fourth pacemakers was 2:1 for most of the trace with an occasional “interpolated” beat (first and last cycles of fourth trace). The relationship between the fourth and fifth traces was 2:1 throughout. The pattern of discharge of the top trace was the most complex, with the cycle length varying continuously.

One can consider the five traces as representing the activity of five separate groups of pacemaker cells comprising the sinoatrial node. Atrial activation, and thus heart rate, would depend upon which of the clusters was serving as the outflow tract to the atrium. When the clusters were well coupled electrically (as in panel B), all fired synchronously, and atrial activation was the same, no matter which cluster served as the outflow tract. However, in the case in which coupling resistance between cells is higher (panel C), atrial rate would be markedly different, depending upon which cluster determined the atrial frequency. For example, if the atrial discharges were determined primarily by the second or third pacemakers, the overt frequency would be high and somewhat arrhythmic. The fourth or fifth traces would produce slower atrial rates, and the top trace would produce a very dysrhythmic pattern of atrial activation. In every case, the frequency and the rhythm would depend upon the degree of cell-to-cell coupling and the phasic interactions between neighboring pacemakers.

**Discussion**

The dynamic interactions of simulated SA node pacemaker “cells” coupled by means of a variable resistance are described in this study. When weakly coupled, the active discharge of one cell produced a subthreshold depolarization in the other. Previous studies have shown that such subthreshold stimuli can prolong or abbreviate the cycle during which they occur (Jalife and Moe, 1976; Sano et al., 1978; Jalife and Michaels, 1985). Such phase-dependent interactions also were observed in the present model, and an ionic mechanism is suggested. Furthermore, no special modifications needed to be made in the original equations (as described by Yanagihara et al., 1980) to obtain phase-dependent behavior. Other mathematical models of pacemaker activity have been reported, including a modification of the McAllister-Noble-Tsien (MNT) model for cardiac Purkinje fibers (Bristol and Clark, 1982, 1983), a single gating variable model (Van Capelle and Durrer, 1980), and a complex model incorporating provisions for extracellular potassium accumulation, electrogenic sodium pumping, and sodium-calcium exchange (DiFrancesco and Noble, 1984). We have chosen to use the Yanagihara model, primarily because it is based on voltage clamp data obtained by a single group of investigators from a sinus node preparation in a single species (see Yanagihara et al. (1980) for references). In addition, in spite of the fact that this model probably oversimplifies the biologic situation (e.g., no provisions are made for extracellular potassium accumulation or for the electrogenic sodium pump), it accurately reproduces many of the phenomena observed in experimental situations (Ypey, 1980; Jalife, 1984; Delmar et al., 1986; Takayanagi and Jalife, 1986). The model has also proven useful for studying acetylcholine-sinus node interactions (Michaels et al., 1984a) and provides a basis for discussing underlying mechanisms.

**Ionic Basis of the Biphasic PRC**

Computer modeling has been used by several authors to study the ionic basis of the phase-response curve. Using their Purkinje fiber model, McAllister et al. (1975) reproduced quite closely the phase resetting behavior demonstrated in the classical experiments of Weidmann (1951). However, no detailed explanation for the phenomenon was given. Bristow and Clark (1982) modified the MNT model to account for the electrical activity of primary pacemaking in the sinus node. Their model simulated phase resetting behavior, and demonstrated that phase advance produced by a depolarizing pulse was the result of activation of $i_s$. Yet, no mechanism was proposed for the ionic basis of phasic delay of weaker and/or briefer pulses applied early in the pacemaker cycle. On the other hand, Clay et al. (1984) recently provided an elegant description of the relationship between phase resetting and the underlying ionic currents, using a model based on voltage clamp analysis of chick ventricular cells. These authors have shown that prolongation of the pacemaker period resulting from current pulses applied in the first half of diastole are largely attributable to changes in the pacemaker current $i_{K1}$. Shortening of the period results from activation of $i_{Na}$.

The present mathematical model mimics the experimental results in the sinus node (Sano et al., 1978; Jalife et al., 1980) to the extent that brief depolarizing current pulses produce a biphasic phase-response curve. In addition, both manipulations employed to reduce intrinsic pacemaker frequency, viz., application of bias hyperpolarizing current and reduction of $i_s$, produce “stronger” and
more symmetrical PRC (Fig. 9) which are consistent with experimental results. The ionic basis of the phase delay and phase advance produced by a depolarizing pulse is suggested from inspection of membrane current records. A transient decrease in $i_s$ and $i_{Na}$ appears to account for the delay of the subsequent discharge (Fig. 5). Indeed, as a result of this decrease, there is a momentary shift in total membrane current ($i_t$) such that it becomes outward just after the current pulse (Fig. 5A). A similar shift was also observed in a previous study when acetylcholine pulses were used (Michaels et al., 1984a). Phase advance is a result of an increase in both $i_s$ and $i_{Na}$. In this latter case, total current never becomes outward (Fig. 5B).

Dynamic Interactions and Mutual Entrainment

Phase dependence is a prerequisite for entrainment of an oscillator by periodically applied brief stimuli, as has been demonstrated in a variety of systems (Winfree, 1980). In the sinus node, the discharge of one pacemaker produces a brief depolarization in its weakly coupled neighbor (Figs. 3 and 4). The frequency effects of this depolarization are phase dependent. This suggests that synchronization of the individual sinus pacemakers might occur via a mechanism of mutual entrainment. According to this hypothesis, the synchronous firing of SA node cells results not from the propagated activity of a "dominant" pacemaker, but from mutual interaction that results in a "democratic consensus" as to when all the cells should fire (Jalife, 1984).

Previous studies have demonstrated mutual entrainment of cardiac pacemakers (DeHaan and Hirakow, 1972; Ypey et al., 1979; DeHaan, 1982; Jalife, 1984; Delmar et al., 1986). Isolated cultured heart cells with different intrinsic frequencies have been shown to synchronize soon after making physical contact (Clapham et al., 1980; DeHaan, 1982). In addition, pairs of cardiac myocytes can synchronize their spontaneous activities through an intermediary inexcitable cell (Goshima, 1975; DeHaan and coworkers have investigated synchronization in pairs of spherical aggregates of chick embryo myocytes when they are brought into close apposition (see DeHaan, 1982, for references). They attributed synchronization to a process of entrainment and not to conduction, or capture, since there was a considerable difference in firing times (latency) between the coupled pacemakers. More recent studies with the sinus node-sucrose gap preparation have demonstrated that two isolated pacemaker foci, separated by the electrically inexcitable tissue in the gap, can be made to synchronize when an external shunt pathway allows for sufficient electrotonic propagation between the foci (Jalife, 1984). The patterns of mutual entrainment can be 1:1, 2:1, or more complex, depending on the value of the shunt resistance, and, hence, on the degree of coupling between the pacemakers. A system of this type was modeled in previous simulations from our laboratory in which two spontaneously active cells were coupled through an inexcitable cell (Jalife and Michaels, 1985; Delmar et al., 1986). Results of the simulations are similar to those obtained in the experimental situation (Delmar et al., 1986). Both the experimental data and the results of the present model support the hypothesis that synchronization occurs by means of mutual entrainment. In addition, the model results suggest a mechanism for this process, namely, the phase-dependent frequency effects of electrotonically mediated depolarizations.

Pacemaker "Dominance"—a Question of Sensitivity

In the present simulations, two methods were used to alter the intrinsic period of one of the coupled pacemakers: (1) applications of bias current, and (2) reduction in the fraction of $i_s$. In both instances, the effect of the faster pacemaker on the slower was greater than that of the slower on the faster. Since both manipulations reduce the relative contribution of $i_s$ to slow diastolic depolarization and enhance the importance of other membrane currents, the slower pacemaker would be expected to be more sensitive to external perturbations (see Fig. 8). The fact that two coupled pacemakers synchronize at a common period that is always closer to the period of the faster pacemaker has been observed in experimental preparations (Takayanagi and Jalife, 1986) and with an electronic model of mutual entrainment (Ypey et al., 1980). From the results obtained here with depolarizing current pulses (Fig. 9) and with the phasic influence of one pacemaker on the other (Fig. 8), it is evident that the PRC are both larger in amplitude and more symmetrical for the slower pacemaker than for the faster. This indicates that the faster pacemaker will always have a greater influence on the slower than the reverse. In addition, there is another explanation for the phenomenon that would be true even if the PRC for the two pacemakers were identical. If one considers the phasic interactions between two pacemakers whose intrinsic frequencies lie within the range of 1:1 to 2:1 (Fig. 1), it is apparent that when both pacemakers discharge initially at the same time, the second discharge of $F$ will occur late in the $S$ period (i.e., at a phase greater than 50%). This results in a major abbreviation of the latter. The phase-advanced $S$ discharge will be closely coupled to the preceding $F$ action potential and thus will fall very early in the $F$ cycle (see also, Takayanagi and Jalife, 1986, their Fig. 8). Hence, the delay in the firing of the faster pacemaker produced by this discharge will be small (Fig. 1). Consequently, whenever stable 1:1 entrainment is maintained, the faster pacemaker will have a stronger influence on the slower than vice versa.

Predicting the Entrained Cycle Length

One of the most important aspects of this study relates to the fact that, under a given set of condi-
tions, the cycle length at which two coupled pacemakers with different intrinsic periods will entrain can be predicted. Indeed, within the constraints of our simulations, the entrained period proved to be a complex function of the F-S cycle length difference (Fig. 10), the coupling resistance, and the phase relations between pacemaker discharges. This suggests that when two or more pacemaker cells are coupled, their aggregate rhythm will not be that of the fastest or "dominant" pacemaker; neither will it be the arithmetic average of the intrinsic pacemaker frequencies. Rather, through their electrotonically mediated interactions, the coupled pacemakers will "reach a consensus" and will mutually entrain each other at a predictable rate. On the basis of such predictability, it is possible to describe the higher order interactions of hundreds of simulated cells arranged in two dimensions (Michaels et al., 1986), and this should lead to a better understanding of the mechanisms of entrainment of the thousands of cells comprising the compact region of the sinus node (Bleeker et al., 1980). For example, as shown in Figure 10B, the difference in the intrinsic periodicity can be extremely important in predicting the level of coupling at which two pacemakers can synchronize in a one-to-one manner. When the difference between $r_S$ and $r_F$ is small, a very low level of coupling is sufficient to maintain synchrony. In a system such as the compact region of the rabbit sinus node, all cells are capable of spontaneous activity, but gap junctional connections are relatively sparse and much smaller than in other heart tissues (Bleeker et al., 1980). However, on the basis of the these simulations, we can predict that mutual entrainment and synchronous firing of pacemakers in this region will be maintained as long as the range of individual intrinsic periods is small, and as long as some degree of electrical coupling is present between cells.

**Development of Arrhythmic Patterns**

The observation that 1:1 entrainment is broken at lower levels of coupling resistance when the difference in intrinsic periods is increased (Figs. 5 and 6) is what might be expected intuitively. As demonstrated elsewhere (Jalife et al., 1980; Jalife et al., 1983), the phase-response curve determines the limits of the zones of stable entrainment. In other words, a given stimulus can only advance or delay the perturbed oscillator by a given maximal amount. When the period of one pacemaker is increased while the period of the other is held constant, stable entrainment is lost, and the pacemakers mutually entrain at a more complex relation. The pattern of 2:1 (F:S) entrainment seen in curve 4 of Figure 6 results from the fact that, over this range of coupling resistances, pacemaker F is continuously accelerated, while pacemaker S is continuously slowed. These changes in periodicity are a consequence of the phasic relations between pacemaker discharges and follow from the phase-response curves. Further increases in coupling resistance produce an F:S firing ratio equal to the intrinsic ratio, since the amplitudes of the PRC are reduced (see Fig. 8).

In a recent report, Joyner et al. (1983) described simulations in which two cells of the Yanagihara type were coupled through an ohmic resistor. When adjusted for differences in cell surface area, the range of coupling resistances used in their study and ours is, in fact, very similar, and several of their observations are confirmed by our results. For example, as coupling resistance is increased, there is an increase in the F-S interval between discharges of the entrained pacemakers (Joyner et al., 1983), their Fig. 6). However, there appear to be some major differences in the results of the two studies. Significantly, Joyner et al. did not report the appearance of complex patterns of interaction at higher levels of coupling resistance. To investigate the possibility that the interaction between a standard pacemaker and one with a shorter intrinsic period produced by increasing $i_o$ is inherently different from that of a normal and a slower pacemaker, we ran a few simulations of this type (not shown). Regardless of the conditions, we found patterns of complex interaction at intermediate levels of coupling resistance. Thus, it remains unclear why there are discrepancies between our results and those of Joyner et al.

The degree of cell-to-cell coupling in cardiac tissues can be decreased by a number of manipulations including hypoxia (Wojtczack, 1979), superfusion with hypertonic solutions (Barr et al., 1965), heptanol (Delezle and Herve, 1983), and cardiac glycosides (Weingart, 1977). Recent studies have shown that most of these agents are capable of producing loss of mutual entrainment between groups of SA pacemaker cells (Jalife, 1984; Delmar et al., 1986; Takayanagi and Jalife, 1986). In this regard, it is well known that superfusion of the isolated sinus node with toxic doses of digitals can induce progressive tachycardia leading to Wenckebach patterns of sinoatrial block and complex rhythm disturbances (Steinbeck et al., 1980). It has long been surmised that these alterations are produced by membrane depolarization and by the release of endogenous neurotransmitters (Brooks and Lu, 1972). Experiments from this laboratory in which the central segment of a sinus node strip was superfused with ouabain in the presence of atropine and propranolol (Takayanagi and Jalife, 1986) produced results similar to those seen with the computer model. Both sets of data suggest that the progressive SA conduction block and the development of arrhythmias may be explained solely on the basis of cellular uncoupling, with resultant changes in pacemaker interactions and entrainment patterns.

We thank Irwin M. Weiner and Mario Delmar for reading the manuscript, and Judy Heffron for preparing the figures. The assistance of Leo Walsh in maintaining the computer hardware and the
secretarial skills of LaVerne Trueman and Joanne Scheible are also appreciated.

This work was supported by Grant HL 29439 from The National Institutes of Health and by Grants-in-Aid from The American Heart Association, Broome County New York and Upstate New York Chap-

ter.

Dr. Jalife is an Established Investigator of the American Heart Association.

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Received November 8, 1985; accepted for publication February 14, 1986.

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INDEX TERMS: Computer models • Phase-response curve • Arrhythmias • Entrainment • Electromotive interactions • Heart rate

Circulation Research/ Vol. 58, No. 5, May 1986
Dynamic interactions and mutual synchronization of sinoatrial node pacemaker cells. A mathematical model.

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Circ Res. 1986;58:706-720
doi: 10.1161/01.RES.58.5.706

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/58/5/706