

0.19 M, 0.1 M, and 0 M. The filter was then incubated for 60 minutes in buffer A supplemented with 5 percent dehydrated Carnation milk and 0.05 percent NP-40 and for another 60 minutes in the same buffer containing 1 percent rather than 5 percent dehydrated Carnation milk. The binding reaction was carried out by adding ³²P-labeled fusion protein to the buffer (10⁶ cpm/ml) and incubating for 12 hours. For labeling fusion protein, the bacterial cells were collected by centrifugation and lysed by repeated freeze and thawing in buffer (20 mM Hepes-KOH, pH 7.5, 50 mM NaCl, 2 mM EDTA, and 0.2 percent deoxycholate). In most cases the fusion proteins represented at least 10 percent of the total bacterial protein. Protein preparations obtained after centrifugation at 12,000g for 20 minutes or further purification steps were incubated at 37°C for 90 minutes in a solution of 20 mM Hepes-KOH, pH 7.5, 100 mM NaCl, 12 mM MgCl₂, 1 mM dithiothreitol (DTT), 100 μCi of [³²P]ATP, and 25 U of heart muscle kinase catalytic subunit (Sigma). The solution containing the phosphoproteins was then dialyzed against a buffer (10 mM Hepes-KOH, pH 7.5, 60 mM KCl, 1 mM EDTA, 1 mM DTT) to remove the unincorporated radioactivity. The specific activity of the ³²P-labeled protein was estimated to be 2.5 to 5.0 × 10⁴ cpm/pmol of the polypeptide.

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28. For immunoblots protein was fractionated by SDS-PAGE and transferred onto a nitrocellulose filter. The filter was incubated in a blocking solution [10 mM Tris, pH 8, 150 mM NaCl, 1 percent Tween 20, 2 percent bovine serum albumin (BSA), 3 percent normal goat serum] for 30 minutes at room temperature. Binding to primary antibodies was effected by adding the rabbit antiserum to the blocking solution and incubating

for 30 minutes at room temperature. The excess unbound antibodies were removed with TST solution (blocking solution without BSA and normal goat serum). The binding to secondary antibodies [horseradish peroxidase (HRP)-conjugated goat antibodies to rabbit immunoglobulin G (Amersham)] was performed in TST solution with a dilution of 1:10,000. The specific antibody binding was visualized by chemiluminescence (ECL system, Amersham).

29. The bacteria cell pellet was resuspended in buffer of 50 mM Hepes-KOH, pH 7.5, 100 mM KCl, 2 mM EDTA, 1 mM DTT, and 0.5 percent deoxycholate. The cell lysate was prepared by sonicating the cell suspension at medium scale twice for 30 seconds. Nucleic acid in the lysate was precipitated by polyamine and cleared by 20 minutes of centrifugation at 10,000g. This starting material was then fractionated on a Fast Protein Liquid Chromatography (FPLC) Mono Q (Pharmacia LKB) column with a 50 mM to 500 mM linear gradient of KCl. The activity was monitored by immunoblot (28) and the activity pool was then fractionated on FPLC phenol Sepharose with a 2 M to 100 mM linear gradient of (NH₄)₂SO₄ or directly purified through affinity column containing antibodies to the FLAG peptide tag (IBI) which recognize the peptide sequence DYKD (Fig. 1A). The activity was then concentrated by hydroxy-

lapitite chromatography. This material was then analyzed on a FPLC Superose 6 column with a buffer containing 25 mM Hepes-KOH, pH 7.5, 0.5 M KCl, 2 mM EDTA, 2 mM DTT, and 5 percent (w/v) glycerol. The fraction collector was activated to collect 500 μl per fraction after the first 5-ml elution. The activity was followed by membrane binding analysis with ³²P-labeled NSHB and quantified by spectrometry.

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Controlling Cardiac Chaos

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The extreme sensitivity to initial conditions that chaotic systems display makes them unstable and unpredictable. Yet that same sensitivity also makes them highly susceptible to control, provided that the developing chaos can be analyzed in real time and that analysis is then used to make small control interventions. This strategy has been used here to stabilize cardiac arrhythmias induced by the drug ouabain in rabbit ventricle. By administering electrical stimuli to the heart at irregular times determined by chaos theory, the arrhythmia was converted to periodic beating.

The realization that many apparently random phenomena are actually examples of deterministic chaos offers a better way to understand complex systems. Phenomena that have been shown to be chaotic include the transition to turbulence in fluids (1), many mechanical vibrations (2), irregular oscillations in chemical reactions (3), the rise and fall of epidemics (4), and the irregular dripping of a faucet (5). Several studies have argued that certain cardiac arrhythmias are instances of chaos (6, 7). This is important because the identification of a phenomenon as chaotic may make new therapeutic strategies possible.

Until recently the main strategy for dealing with a system displaying chaos was to develop a model of the system sufficiently detailed to identify the key parameters and then to change those parameters enough to

take the system out of the chaotic regime. However this strategy is limited to systems for which a theoretical model is known and that do not display irreversible parametric changes (often the very changes causing the chaos) such as aging.

Recently a strategy has emerged that does not attempt to take the system out of the chaotic regime but uses the chaos to control the system. The key to this approach lies in the fact that chaotic motion includes an infinite number of unstable periodic motions (8). A chaotic system never remains long in any of these unstable motions but continually switches from one periodic motion to another, thereby giving the appearance of randomness. Ott, Grebogi, and Yorke (OGY) (9) postulated that it should be possible to stabilize a system around one of these periodic motions by using the defining feature of chaos, the extreme sensitivity of chaotic systems to perturbations of their initial conditions.

The OGY theory was first applied experimentally to controlling the chaotic vibrations of a magnetoelastic ribbon (10) and subsequently to a diode resonator circuit

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(11) and to the chaotic output of lasers (12). We have found that it is possible to control a chaotic cardiac arrhythmia using the same basic properties of chaotic systems that were exploited by OGY but that are here employed in a new method of chaos control suitable for use in systems where no systemwide parameters can be readily manipulated as required by the OGY method.

Experimental arrhythmia model. Our cardiac preparation consisted of an isolated well-perfused portion of the interventricular septum from a rabbit heart, arterially perfused through the septal branch of the left coronary artery with a physiologic oxygenated Krebs's solution at 37°C (13). The heart was stimulated by passing a 3-ms constant-voltage pulse, typically 10 to 30 V, at twice the threshold between platinum electrodes embedded in the preparation, by means of a Grass SD9 stimulator triggered by computer. Electrical activity was monitored by recording monophasic action potentials with Ag-AgCl wires on the surface of the heart. Monophasic action potentials and a stimulus marker tracing were recorded on a modified videocassette recorder (Model 420, A. R. Vetter, Inc.) and one of the monophasic action potential traces was simultaneously digitized at 2 kHz by a 12-bit A-D converter board (National Instruments model AT-MIO-16). The digitized trace was processed in real time by a computer to detect the activation time of each beat from the maximum of the first derivative of the voltage signal.

Arrhythmias were induced by adding 2 to 5 μM ouabain with or without 2 to 10 μM epinephrine to the arterial perfusate. The mechanism of ouabain-epinephrine-induced arrhythmias is probably a combination of triggered activity and nontriggered automaticity caused by progressive intracellular Ca^{2+} overload from Na^+ pump inhibition and increased Ca^{2+} current (14, 15). We reasoned that this arrhythmia might progress to chaos because in cardiac myocytes intracellular Ca^{2+} is regulated by several interactively coupled processes whose delicate balance is disrupted by ouabain. The resultant oscillations in intracellular Ca^{2+} cause spontaneous beating by activating arrhythmogenic inward currents from electrogenic Na^+ - Ca^{2+} exchange and Ca^{2+} -activated nonselective cation channels (14). Typically the ouabain-epinephrine combination induced spontaneous beating, initially at a constant interbeat interval and then progressing to bigeminy and higher order periodicity before developing a highly irregular aperiodic pattern of spontaneous beating in ~ 85 percent of the preparations. The duration of the aperiodic phase was variable, lasting up to several minutes before spontaneous electrical activity irreversibly ceased, probably correspond-

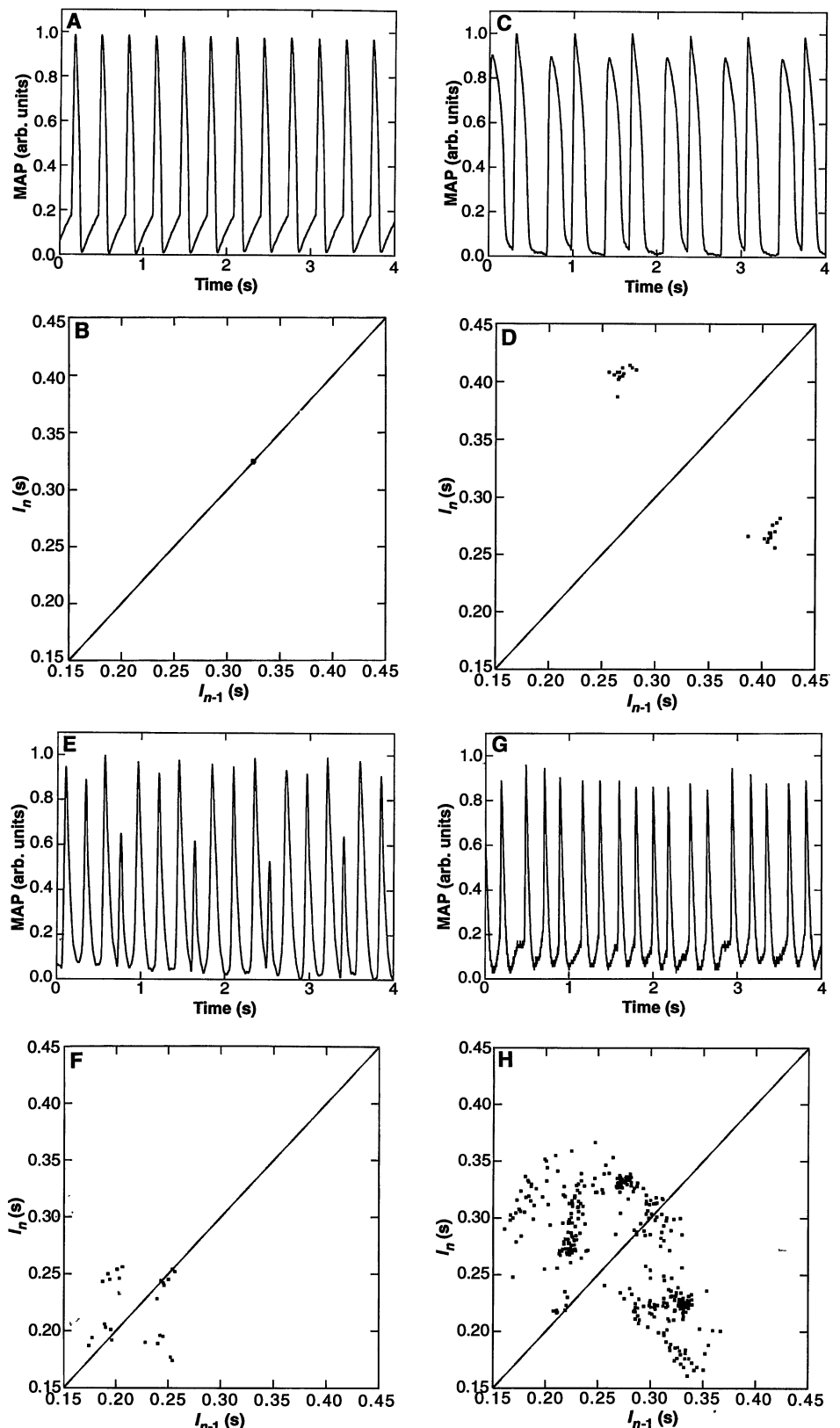


Fig. 1. Recordings of monophasic action potentials (MAPs) (A, C, E, and G) and their respective Poincaré maps of interbeat intervals (B, D, F, and H) at various stages during arrhythmias induced by ouabain-epinephrine in typical rabbit septa. Typically the arrhythmia was initially characterized by spontaneous periodic beating at a constant interbeat interval (A and B), then developed bigeminal or period 2 patterns (C and D) or higher order periodicities such as a period 4 pattern (E and F), and lastly a completely aperiodic pattern (G and H). Note that in the Poincaré map of the final stage the points form an extended structure that is not point-like or a set of points (that is, not periodic) and is not space-filling (that is, not random). This is a sign of chaos.

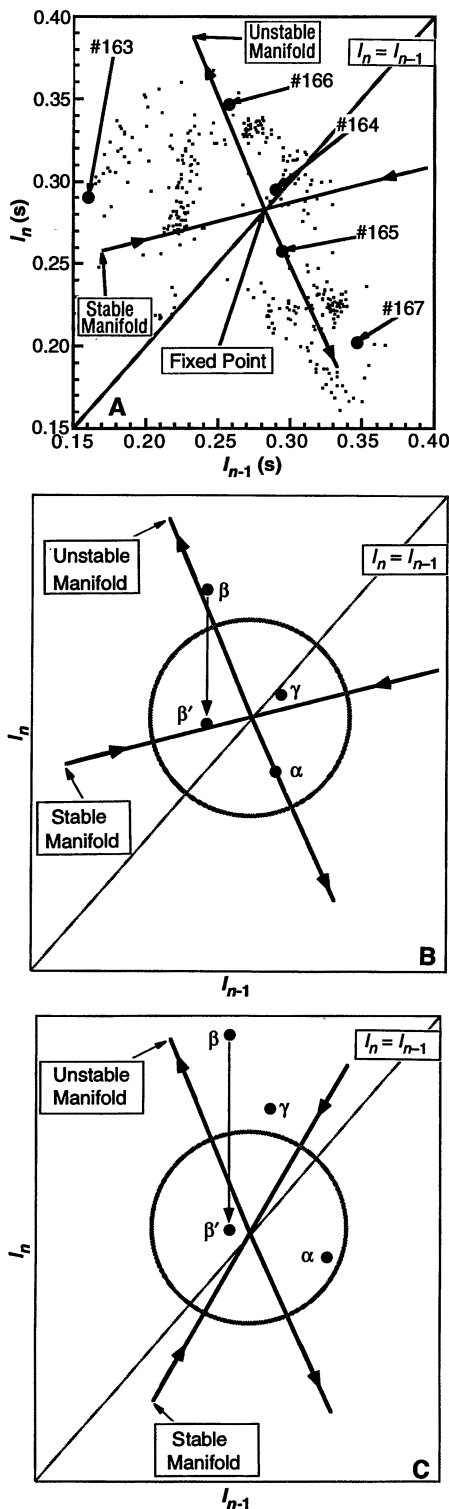


Fig. 2. (A) The Poincaré map of the aperiodic phase of a ouabain-epinephrine-induced arrhythmia in a typical heart preparation illustrating the structure of the chaotic attractor. (B) Blowup of the Poincaré map in the region of the unstable fixed point illustrating schematically the idealized chaos control method. (C) A schematic of the actual implementation achieved with chaos control. Note that the stable manifold has shifted, a common variation among data runs. The circles in (B) and (C) enclose the region about the fixed point in which chaos control is enabled.

ing to progressive severe membrane depolarization from Na^+ pump inhibition. The spontaneous activity induced by ouabain-epinephrine in this preparation showed a number of features symptomatic of chaos. Most important, in progressing from spontaneous beating at a fixed interbeat interval to highly aperiodic behavior, the arrhythmia passed through a series of transient stages that involved higher order periodicities. These features are illustrated in Fig. 1, in which the n th interbeat interval (I_n) has been plotted against the previous interval (I_{n-1}) at various stages during ouabain-epinephrine-induced arrhythmias. Such a Poincaré map (5) allows us to view the dynamics of the system as a sequence of pairs of points (I_{n-1} , I_n), thus converting the dynamics of our system to a map. This map has several special features. The first is that a periodic motion appears as a finite set of points in such a plot (Fig. 1, A to C). When the arrhythmia progressed to the aperiodic stage, truly random aperiodicity would have demonstrated no structure in the Poincaré map. Chaotic aperiodicity however is represented by an extended structure that is not a single point (or finite set of points) and yet is not space-filling. Figure 1D illustrates that the aperiodic phase of the ouabain-epinephrine-induced arrhythmia fell into the latter category, supporting a chaotic rather than a random process. In 11 preparations the Poincaré maps consistently showed patterns similar to Fig. 1D, and these patterns are consistent with chaotic aperiodicity. Figure 1, A to D, as shown are from different preparations. However virtually all preparations exhibited at least one period doubling before the arrhythmia became chaotic (although it is not clear whether the transitions to chaos in our preparations are the result of a period doubling route to chaos).

Method of chaos control. The control of chaos begins with the realization that, where the attractor crosses the line of identity ($I_n = I_{n-1}$), it must contain an unstable periodic motion of period 1. (If it were stable, the attractor would be only a single point lying on the diagonal of Fig. 1). Such a crossing point is called an unstable fixed point and represents constant interbeat intervals (with period 1). These unstable fixed points have associated directions along which the trajectory approaches and diverges from the fixed point. These directions are called the stable and unstable manifolds, respectively. A typical sequence of interbeat intervals during aperiodic beating induced by ouabain-epinephrine in a rabbit septum is indicated in Fig. 2A (points 163 through 167). From point 163 to 164 the state of the system (or state point) moves toward the unstable fixed point. Thus point 163 must lie close to the

stable manifold (direction). Points 164 through 167 diverge from the unstable fixed point and hence reveal an unstable manifold (direction). In the chaotic region unstable fixed points on the attractor possess at least one unstable and one stable manifold (16). Thus the local geometry around a fixed point in a Poincaré map plot is that of a saddle. In this case the saddle is a flip saddle; that is, while the distances of successive state points from the fixed point increase in an exponential fashion along the unstable manifold (one of the signs of chaos) the state points alternate on opposite sides of the stable manifold (17). The flip saddle appears as a short interbeat interval followed by a long interval and vice versa.

Our method of chaos control, which we call proportional perturbation feedback (PPF), consists of delivering a perturbation (near the desired fixed point) that forces the system state point onto the stable manifold of the desired fixed point. Consequently the system will naturally move toward the unstable fixed point rather than away from it. Contrast this with the OGY method, which moves the stable manifold to the current system state point rather than vice versa. Both methods use a linear approximation of the dynamics in the neighborhood of the desired fixed point. OGY then varies a systemwide parameter to move the stable manifold to the system state point; our method perturbs the system state point to move it toward the stable manifold. Thus the magnitude of our perturbation is the same as predicted by the OGY equations, but the sign is opposite. We developed the PPF method when it became obvious that our cardiac preparation possessed no systemwide parameter that could be changed sufficiently quickly to implement classical OGY control.

The procedure begins by determining the location of the unstable fixed point ξ_F , as well as its local stable and unstable contravariant eigenvectors, f_s and f_u respectively. If ξ_n is the current position of the system on the Poincaré map and p is the predicted timing of the next natural beat, the required advance in timing δp is proportional to the projection of the distance $\xi_n - \xi_F$ onto the unstable manifold (the unstable contravariant eigenvector):

$$\delta p = C(\xi_n - \xi_F) \cdot f_u \quad (1)$$

where:

$$C = \frac{\lambda_u}{\lambda_u - 1} \frac{1}{g \cdot f_u} \quad (2)$$

The constant of proportionality C depends on the unstable eigenvalue λ_u . This eigenvalue determines the rate of the exponential divergence of the system from the fixed point along the unstable manifold and is

easily determined (8) from the sequence of points 164 through 167 in Fig. 2A. Lastly, g is the sensitivity of points near the fixed point to an advance in the timing δp , which we approximate with the change in the fixed point with respect to δp :

$$g \approx \frac{\delta \xi_F}{\delta p} \quad (3)$$

The constant C is inversely proportional to the projection of this change onto the unstable manifold.

We must stress that Eqs. 1 to 3 are identical to the OGY control equations except that the systemwide parameter p used in the OGY method is replaced in our method by the variable that controls the system perturbation. Thus our system perturbation δp (which replaces the change, δp , in the OGY systemwide parameter) represents the amount of time we must shorten an anticipated natural beat (through the introduction of a stimulus) to force the state point onto the stable manifold.

Our proportional perturbation feedback control consisted of two parts: a learning phase and an intervention phase. In the learning phase the computer monitored the interbeat intervals until it determined the approximate locations of the unstable fixed point and the stable and unstable manifolds (9, 10). The application of Eqs. 1 and 2 during the intervention phase was then straightforward once the geometry of the local map around the fixed point had been determined and the quantity g had been found. The interbeat interval was directly manipulated by shortening it with an electrically stimulated beat. The advance in the timing of the next interbeat interval is the perturbation δp . The sensitivity of the state point to changes in p was determined experimentally by noting the change in the interbeat interval in response to a single electrical stimulus when the state point was near the fixed point (Eq. 3).

Chaos control with this approach was complicated by the fact that the intervention was, of necessity, unidirectional; that is, by delivering an electrical stimulus before the next spontaneous beat, the interbeat interval could be shortened but it could not directly be lengthened. This is because a stimulus that elicits a beat from the heart must, by definition, shorten the interbeat interval between the previous spontaneous beat and the beat elicited by the stimulus. Although a stimulus that does not elicit a beat may prolong the interbeat interval by electrotonic effects, in the intact heart this is highly dependent both on the precise location of the pacing site in relation to the site of origin of the arrhythmia and on the history of preceding interbeat intervals. Thus such a stimulus is highly unstable and unpredictable during

an aperiodic rhythm and therefore is unsuitable as a cardiac pacing strategy.

The learning phase typically lasted from

5 to 60 seconds, after which the computer waited for the system to make a close approach to the unstable fixed point (indi-

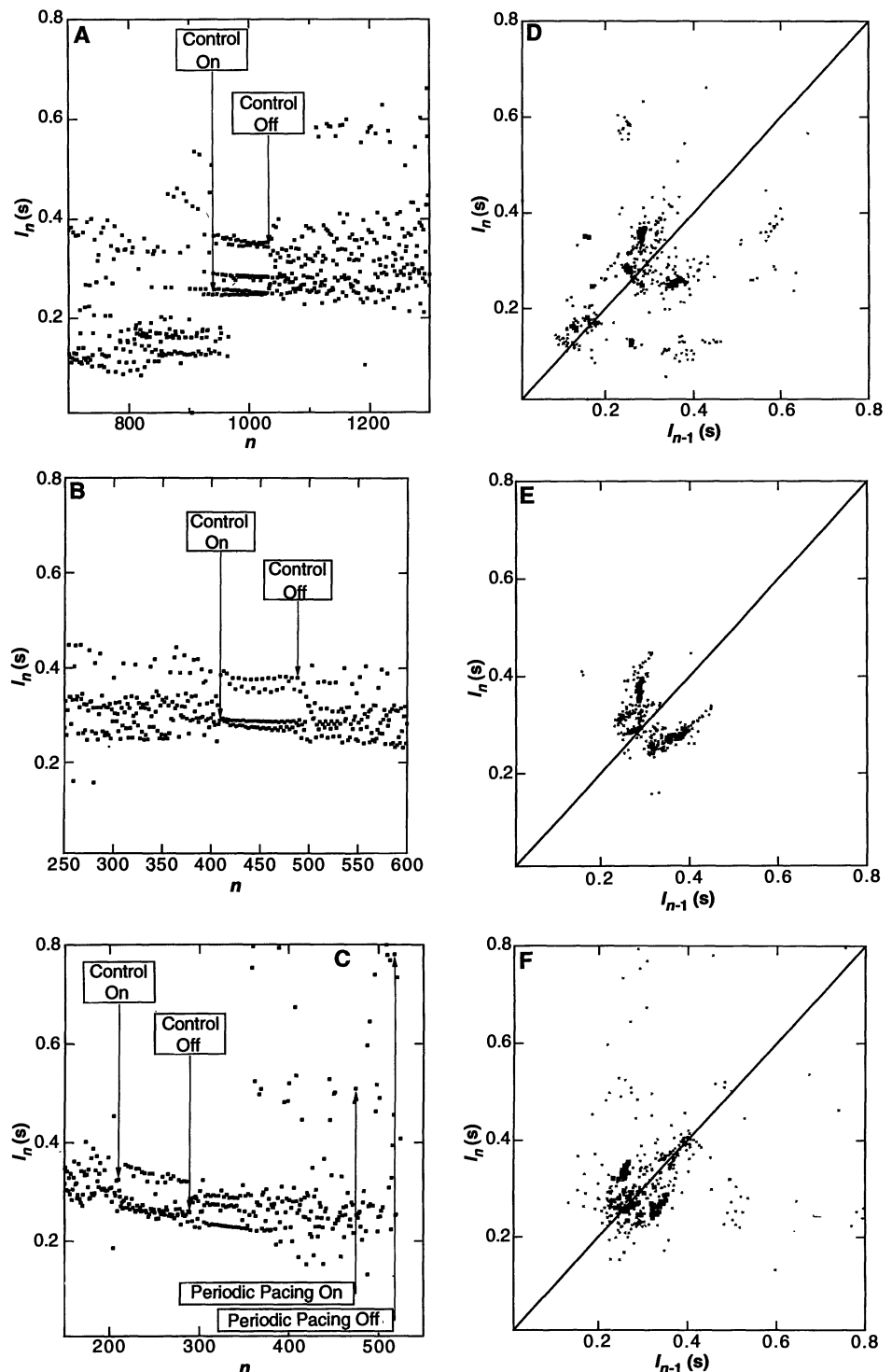


Fig. 3. (A, B, and C) Interbeat interval I_n versus beat number n during the chaotic phase of the ouabain-epinephrine-induced arrhythmia in three typical hearts. The region of chaos control is indicated. In (C) a region during which periodic pacing was applied is also indicated. Note that periodic pacing failed to control the arrhythmia. (D, E, and F) The corresponding Poincaré maps for (A), (B), and (C), respectively. The small points represent interbeat intervals during the uncontrolled arrhythmia, while the larger points represent interbeat intervals during the chaos control. In the (A) and (D) data set, there were several losses of control that occurred early in the control sequence (indicated by the lower points in the early part of the control region). These were always immediately followed by reacquisition of the chaos control.

cated by the point α within the circle in Fig. 2B.) The next point would normally fall further out along the unstable manifold (as well as on the opposite side of the stable manifold) as indicated by point β . However at this point the computer intervened by injecting an electrical stimulus early enough so that this point actually occurred at β' , lying directly below β and, by construction, near the stable manifold. Because the system now lay close to the stable manifold, ideally the subsequent beat would tend to move closer to the fixed point along the stable manifold, as indicated by the point γ . Thus the state point would be confined to the region near the unstable fixed point, thereby regularizing the arrhythmia. However, in actual practice this degree of accuracy was not typically obtained. Figure 2C illustrates the usual result. When β' did not fall precisely on the stable manifold, γ often was not extremely close to the fixed point (fell outside the circle) but still lay fairly close to the stable manifold (since β' was close to the stable manifold). Yet γ lay closer to the stable manifold than point α did. Thus the next point fell within the circle in the vicinity of α and restarted the cycle (as a new point α). As these patterns repeated, a period 3 beating resulted. In this manner the chaotic (arrhythmic) beating was made periodic by only intermittent stimuli. The subsequent stabilized period 3 motion represents the combined dynamics of the cardiac tissue, sensor, and computer control. We emphasize that this approach did not require any theoretical model of the heart; all of the quantities needed were calculated in real time from the data. It should also be noted that a control stimulus has only a transient effect on the cardiac preparation (which may influence the timing of several subsequent beats) but otherwise does not affect the preparation in any permanent fashion.

Results of chaos control. Using PPF, control of the chaotic phase of the ouabain-epinephrine-induced arrhythmia was attempted in 11 separate experimental runs and was successful in 8. Figure 3 shows the results of three successful cases. When the arrhythmia became chaotic, the chaos control program was activated. Our criteria for chaos were that the Poincaré map exhibit stable and unstable manifolds with a flip saddle along the linear part of the unstable manifold (18). Specifically we looked for the state point to walk toward the unstable fixed point along one direction (thereby determining the stable manifold) and then to walk out from the unstable fixed point along a clearly different direction (the unstable manifold). The program then chose and delivered electrical stimuli as described above. In order to prove that we had achieved and maintained control of the

chaos [defined as a clear conversion of a chaotic sequence to a periodic one with a low-integer (2 to 3) period], we turned off the chaos control program and consistently saw a return to chaotic behavior, sometimes preceded by transient complex periodicities, as in Fig. 3C.

Several observations should be made about the pattern of the stimuli delivered by the chaos control program. First, these stimuli did not simply overdrive the heart. Stimuli were delivered sporadically, not on every beat and never more than once in every three beats on average. The pattern of stimuli was initially erratic and aperiodic but soon became approximately periodic as the arrhythmia was controlled into a nearly periodic rhythm. For example, in Fig. 3, the chaos control program rapidly converted the aperiodic behavior of the arrhythmia to a period 3 rhythm. In contrast, periodic pacing, in which stimuli were delivered at a fixed rate, was never effective at restoring a periodic rhythm and often made the aperiodicity more marked. This is illustrated in Fig. 3C, in which the chaos control program converted chaotic behavior to an approximate period 3, whereas periodic pacing at a rate of 75 beats per minute (nearly identical to the time-averaged rate at which stimuli were delivered during chaos control) had no effect. Irregular pacing was similarly ineffective at converting chaotic to periodic behavior, as illustrated in Fig. 3A. In this case chaotic behavior was converted to a period 3 by the chaos control program, but the rhythm quickly became aperiodic again when the parameters of the algorithm were modified by arbitrarily changing C (Eqs. 1 and 2) to eliminate effective chaos control (at the arrow labeled "control off").

In two cases, one of which is shown in Fig. 3A, chaos control had the additional effect of eliminating the shortest interbeat intervals, hence reducing the average rate of the tachycardia. Without an understanding of the chaotic nature of the system, it would seem paradoxical that an intervention that only shortened the interbeat intervals lengthened the average interval. However, because very long interbeat intervals tend to be followed by very short interbeat intervals (a consequence of the properties of a flip saddle), elimination of the very long intervals also tends to eliminate very short intervals. In cases in which very short intervals predominate during the arrhythmia, their elimination during chaos control will tend to lengthen the average interbeat interval.

Future possibilities for chaos control. In the cases where chaos was successfully controlled, the chaotic pattern of the arrhythmia was converted to a low-order periodic pattern. However, as discussed pre-

viously for Fig. 2, B and C, we did not observe any period 1 patterns during chaos control. There is no a priori reason why a period 1 pattern cannot be achieved; once period 3 chaos control is established, it is possible that a refinement of the control parameters could "walk" the points along the stable manifold, in essence spiraling in toward the fixed point. This could be implemented in the future either as a second learning phase in which the details of the Poincaré map are learned to higher accuracy than during the first attempts at chaos control or as an adaptive algorithm that responds to the state of the heart after each beat. An adaptive algorithm might also allow chaos control to adapt to changing physiological conditions such as variations in autonomic tone or other extracardiac factors. It may even be possible to use chaos control to walk the fixed point upward along the diagonal (19), thereby reducing the rate of the tachycardia.

The relevance of the ouabain-induced arrhythmia model used in our study to clinically important arrhythmias in humans is not established. Although toxicity from cardiac glycosides is a common cause of human arrhythmias, only in lethal doses would it be likely to produce the severe aperiodic arrhythmias observed in our study. However many clinically important rapid cardiac arrhythmias are aperiodic, such as atrial and ventricular fibrillation, polymorphic ventricular tachycardia, and multifocal atrial tachycardia. In cases where aperiodic arrhythmias are examples of deterministic chaos, it is conceivable that a chaos control strategy, perhaps implemented by a "smart" pacemaker, could be used to restore the cardiac rhythm to normal. In this context it is encouraging to note that in several instances in which chaos control was achieved in the ouabain-induced arrhythmia model, the average heart rate decreased as a result of the elimination of very short interbeat intervals (Fig. 3). It remains a challenge to determine whether this chaos control strategy in in vitro cardiac ventricle can be successfully applied to the in vivo heart.

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"Thom wants to prove Newton's law— 'A body at rest, tends to remain at rest'."