Editorial

Fibrillation has been classically defined as highly disorganized electrical activity resulting in ineffective contraction of the atria or ventricles. Its consequences are dire, as ventricular fibrillation is the arrhythmia primarily responsible for sudden cardiac death, and atrial fibrillation is associated with significant morbidity and mortality. Recently, the traditional views of fibrillatory mechanisms have been challenged by high resolution mapping studies that reveal spatiotemporally organized wavefronts, including spiral waves traversing the myocardium at the onset of ventricular tachycardia/fibrillation (1, 2). In this issue of *The Journal*, Garfinkel et al. (3) provide evidence that, in the heart, multifrequency oscillations in rhythm and amplitude create a highly unstable prefibrillatory condition exhibiting characteristics similar to those observed in fluids as they undergo transition to the chaotic state of turbulence.

The authors used a battery of analytical tests from nonlinear dynamics in three physiologically stable biologic preparations; namely, chronic human atrial fibrillation, stabilized canine ventricular fibrillation, and fibrillation-like activity in thin epicardial sheets from both species. In addition, a computer model of the fibrillatory state was created based on the biological data and subjected to parallel analysis. The Poincaré plot was employed to compare beat-to-beat intervals and resulted in a ringlike pattern, suggesting the convergence of several oscillations and consistent with deterministic nonrandom behavior. The quasiperiodic basis of the ringlike pattern was verified by Fourier analysis of interval sequences. Circle maps of data from computer simulations and epicardial sheet preparations implicated torus breakdown as the pathway from quasiperiodicity to the chaoslike state. Sensitivity to initial conditions, a hallmark of chaotic behavior, was indicated by calculations of positive Lyapunov exponents in the computer simulation studies, but the biological data appeared to be too coarse to permit calculation of the Lyapunov exponent, an observation that would be suggestive that this measure may not be applicable to biological data. Further evidence of determinism and quasiperiodicity in the transition to fibrillation was also indicated by the development of alternans. Taken collectively, these results provide a cogent case for the existence of deterministic behavior in the development and maintenance of fibrillation and underscore the electrically destabilizing effect of modulated oscillations on the heart.

The present observation is the first demonstration implicating chaotic behavior in fibrillation in human and canine hearts. The most cogent previous evidence of chaotic behavior in arrhythmia (namely, that it results from deterministic mechanisms that are highly sensitive to initial conditions) has been limited to isolated tissue and cardiac cell preparations (1, 4, 5). Kaplan and Cohen (6) were unable to identify a low dimensional attractor in the precordial signal of canine ventricular fibrillation and thus questioned the role of chaos in fibrillation. Goldberger et al. (7) detected a narrow-band frequency spectrum in epicardial and body surface canine ventricular fibrillation rather than the broadband spectrum that they anticipated in a chaotic system. The present authors argue that their positive findings are due to local recording of electrocardiographic data and to employing hemodynamically stabilized preparations. However, it must be kept in mind that fibrillation was artificially induced in the animal models of the present study as it involved electrical stimuli delivered with and without concurrent administration of the potassium channel opener cromakalim. Thus, a major challenge for the future is to demonstrate the presence of chaotic behavior in ventricular fibrillation in the unstable conditions that commonly give rise to ventricular fibrillation, namely acute myocardial ischemia on a background of enhanced sympathetic activity. The possibility that chaotic behavior occurs under pathophysiologically relevant conditions is suggested by the presence of ischemia-induced T-wave alternans, a period-doubling first-order bifurcation, preceding the development of ventricular fibrillation (8).

Overall, the observations of Garfinkel et al. (3) carry important diagnostic and therapeutic implications. With respect to the former, they suggest that complex or quasiperiodic oscillatory behavior presages fibrillation. Alternans was observed at the core of the spiral wave pattern. Its modulation increased in amplitude and period for a few seconds preceding the abrupt onset of fibrillation. They interpreted this finding as evidence that alternans is an expression of electrophysiologic quasiperiodicity and as such is fundamentally linked to fibrillation. The authors further suggest that depolarization alternans reflects an important form of oscillatory behavior that heralds the onset of ventricular fibrillation. Because depolarization and repolarization are closely coupled events, T-wave alternans may have been present although unmeasured in the current studies. This possibility deserves further investigation because repolarization or T-wave alternans has been shown to provide an index of vulnerability to ventricular tachycardia and fibrillation under diverse pathophysiologic conditions (8–10).

The authors postulate that inhibition of complex oscillations by pharmacologic or pacing inventions should exert an antifibrillatory effect. An intriguing concept is proposed that the deactivation kinetics of delayed rectifier potassium currents, recovery from inactivation of inward currents, and intracellular cycling of calcium could offer promising targets for pharmacologic suppression of arrhythmias by interruption of ionic oscillatory behavior. Several investigators have provided evidence that calcium channel blockers are capable of suppressing electrical alternans and ischemia-induced ventricular tachyarrhythmias (11, 12). A particularly innovative approach by Garfinkel et al. (4) was inhibition of oscillations and suppression of ouabain-induced cardiac arrhythmias by electrical pacing strategies programmed on the basis of chaos–control theory. These observations underscore the opportunity to intervene by manipulating a single factor at the root of the complicated electrical behavior of fibrillation. The general applicability of this approach to suppress other forms of ventricular tachycardia and fibrillation remains to be established.

From a broad perspective, the study by Garfinkel et al. (3) represents an important advance signifying that fibrillation is

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not a random but a deterministic process and is probably the result of complex oscillations due to the influence of disease on transmembrane and intracellular ion flux. The findings further serve to illustrate the insights that can be derived from application of nonlinear analytical methods to cardiac signals and to highlight their potential diagnostic and clinical utility.

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References

1. Davidenko, J.M., A.M. Pertsov, R. Salomonsz, W. Baxter, and J. Jalife. 1991. Stationary and drifting spiral waves of excitation in isolated cardiac tissue. *Nature* (*Lond.*). 355:349–351.

2. Bayly, P.V., E.E. Johnson, P.D. Wolf, H.S. Greenside, W.M. Smith, and R.E. Ideker. 1993. A quantitative measurement of spatial order in ventricular fibrillation. *J. Cardiovasc. Electrophysiol.* 4:535–546.

3. Garfinkel, A., P.-S. Chen, D.O. Walter, H.S. Karagueuzian, B. Kogan, S.J. Evans, M. Karpoukhin, C. Hwang, T. Uchida, M. Gotoh, et al. 1997. Quasi-periodicity and chaos in cardiac fibrillation. *J. Clin. Invest.* 99:305–314.

4. Garfinkel, A., M.L. Spano, W.L. Ditto, and J.N. Weiss. 1992. Controlling cardiac chaos. *Science* (*Wash. DC*). 257:1230–1235.

5. Guevara, M.R., L. Glass, and A. Shrier. 1981. Phase locking, period-doubling bifurcations, and irregular dynamics in periodically stimulated cardiac cells. *Science* (*Wash. DC*). 214:1350–1353.

6. Kaplan, D.T., and R.J. Cohen. 1990. Is fibrillation chaos? *Circ. Res.* 67: 886–892.

7. Goldberger, A.L., V. Bhargava, B.J. West, and A.J. Mandell. 1986. Some observations on the question: is ventricular fibrillation "chaos"? *Physica*. 19D: 282–289.

8. Nearing, B.D., A.H. Huang, and R.L. Verrier. 1991. Dynamic tracking of cardiac vulnerability by complex demodulation of the T-wave. *Science* (*Wash. DC*). 252:437–440.

9. Konta, T., Y. Ikeda, M. Yamaki, K. Nakamura, K. Honma, I. Kubota, and S. Yasui. 1990. Significance of discordant ST alternans in ventricular fibrillation. *Circulation*. 82:2185–2189.

10. Rosenbaum, D.S., L.E. Jackson, J.M. Smith, H. Garan, J.N. Ruskin, and R.J. Cohen. 1994. Electrical alternans and vulnerability to ventricular arrhythmia. *N. Engl. J. Med.* 330:235–241.

11. Clusin, W.T., M.R. Bristow, D.S. Baim, J.S. Schroeder, P. Jaillon, P. Brett, and D.C. Harrison. 1982. The effects of diltiazem and reduced serum ionized calcium on ischemic ventricular fibrillation in the dog. *Circ. Res.* 50:518–526.

12. Nearing, B.D., J.J. Hutter, and R.L. Verrier. 1996. Potent antifibrillatory effect of combined blockade of calcium channels and 5-HT_2 receptors with nexopamil during myocardial ischemia and reperfusion in canines: comparison to diltiazem. *J. Cardiovasc. Pharmacol.* 27:777–787.