Electrical Restitution, Critical Mass, and the Riddle of Fibrillation

ROBERT F. GILMOUR, JR., PH.D., and DANTE R. CHIALVO, M.D.*

From the Department of Biomedical Sciences, Cornell University, Ithaca; and the *Center for Studies in Physics and Biology, The Rockefeller University, New York, New York

The elusive riddle of ventricular fibrillation (VF) has been approached from many creative angles. The latest, presented by Wu et al.[1] in this issue of *JCE*, examines the effects of restitution properties on the "critical mass," i.e., the minimum size of cardiac tissue capable of sustaining fibrillation. What is noteworthy about this novel effort is that the very basis for the working hypothesis is rooted in deep mathematical concepts, a brief and highly selective chronological account of which we attempt here, because it has interesting aspects.

The trail begins with Nolasco and Dahlen,[2] who in 1968 used a straightforward graphical technique to demonstrate that, under certain conditions, electrical alternans was a dynamic consequence of the slope of the restitution relation for action potential duration (APD). If the slope of the APD restitution relation (the relation between APD and the preceding diastolic interval) was ≥ 1, APD alternans was possible, whereas if the slope was < 1, it was not.

More than a decade later, Michael Guevara and colleagues[3] took the important step of formalizing Nolasco and Dahlen's graphical method as a one-dimensional difference equation, thereby revealing the correspondence between APD alternans in the experimental system and period-doubling bifurcations in the equations. The strategy of reducing the problem to (the iteration of) a one-dimensional difference equation pioneered by the McGill groups has had wide application, as detailed by Glass and Mackey.[4]

The difference equation method subsequently was adapted further to explain periodic and chaotic rhythms in Purkinje fibers and ventricular muscle.[5,6] The approach was fruitful to the point that it was possible to predict any of a wide variety of rhythms exhibited by periodic stimulation of cardiac tissue,[7-11] where the APD restitution was relevant to the dynamics. In addition, the analytical insight gained by using this approach prompted the contemporaneous observations that the potential antiarrhythmic/proarrhythmic effects of some agents might be explained "on the basis of a decrease/increase in the slope of the APD restitution at very short coupling intervals"[10] and that "it might be possible in the future to reduce the incidence of arrhythmias by pharmacologically modifying the steep left-hand portion of the restitution curve."[8]

Once the dynamics under repetitive stimulation was understood, tackling the larger problem of fibrillation could be attempted. One such attempt occurred in 1990, when a simple question, posed at least once previously (on page 157 of Glass and Mackey[4]), became firmly entrenched in Alain Vinet's mind during one of his many biweekly car trips through the snowbelt connecting Syracuse with Montreal. The following week he was asking colleagues on both sides of the St. Lawrence river: "Imagine this hypothetical experiment: A circulating wave of excitation is set up in a thin ring of tissue. As time passes you reduce very slowly the length of the ring. Which kind of dynamic will you observe: a) if the excitable tissue is nerve-like (no electrical restitution, i.e., APD is constant); and b) if the excitable tissue is cardiac-like (electrical restitution present)?"

Attempts to answer this simple question, with all of its ramifications, would engage researchers for the remainder of the decade. Interest in such a question was motivated by the fact that the problem of wave propagation in two dimensions could be visualized as waves circulating on a track of laterally interconnected rings (much like a slice of onion). Thus, a good grasp of the "ring

J Cardiovasc Electrophysiol, Vol. 10, pp. 1087-1089, August 1999

Address for correspondence: Robert F. Gilmour, Jr., Ph.D., Department of Physiology, Cornell University, 724 Veterinary Research Tower, Ithaca, NY 14853-6401. Fax: 607-253-3851

Manuscript received 28 May 1999; Accepted for publication 31 May 1999.

case study" was expected to help illuminate the big picture in two dimensions. Very soon, at least three groups concluded more or less simultaneously that the rich complex dynamics seen in (simulated) cardiac-like rings was connected with the nonlinearity in the early portion of the APD restitution relation.[12-16]

The numerical simulations made it readily apparent that wave circulation on a ring was not stable under these "cardiac-like" conditions.[16] Consequently, in the two-dimensional scenario, APD alternans at short cycle lengths caused degeneration of a single spiral wave into complicated multiple wavelets. The lack of spiral wave stability in the simulations was something of a puzzling paradox to those excited by the report of the first (remarkably stable) spiral waves produced experimentally in sheep ventricular muscle.[17] Perhaps the sheep did not read the book wherein the hard theoretical calculations were written, or perhaps more careful measurements of the properties of the restitution relation were called for before initiating the spirals. Even today, the quantitative values of such a relation are not known with sufficient precision to "close the book" on questions such as whether it is possible to establish something more than stable spirals (VF?) in a two-dimensional piece of normal cardiac tissue. Neither are we able to anticipate theoretically the results of Wu et al.[1]

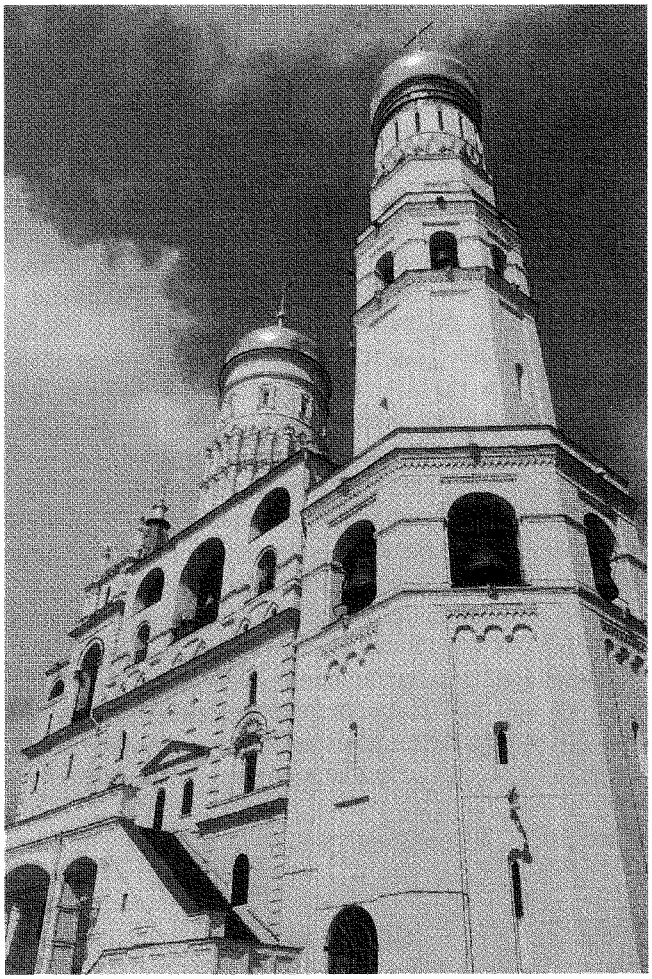
This situation may be changing, however, as a result of recent experimental studies.[18,19] First, it is now clear that the method used to measure APD restitution importantly influences the results. Consequently, the very definition of the APD restitution relation may need to be revised. When measured dynamically, the slope of the APD restitution relation is > 1 during constant pacing and during actual and simulated VF. Moreover, drugs that reduce the slope of the APD restitution relation (at least those tested so far) prevent the induction of VF and convert preexisting VF into a periodic rhythm, presumably by stabilizing a single spiral wave and thereby preventing its degeneration into many self-perpetuating waves. These results, which are in stark contrast to the prevailing notion that prolongation of refractoriness or slowing of conduction are the keys for prevention of VF, may indicate a new direction for the development of antifibrillatory drugs.

But much remains to be done. We still know very little about the quantitative details of APD restitution in different regions of the heart under conditions relevant to the initiation of VF. Our ignorance in this area is reflected by the lack of a good understanding of the mechanism by which certain drugs or disease states promote VF, and by our inability to identify more than a handful of drugs that prevent VF. And so, despite many fanciful advances, the understanding of fibrillation (as Winfree[20] has pointed out) is not yet in the bag.

References

1. Wu T-J, Yashima M, Doshi R, et al: Relation between cellular repolarization characteristics and critical mass for human ventricular fibrillation. J Cardiovasc Electrophysiol 1999;10:1077-1086.
2. Nolasco JB, Dahlen RW: A graphic method for the study of alternation in cardiac action potentials. J Appl Physiol 1968;25:191-196.
3. Guevara MR, Ward G, Shrier A, et al: Electrical alternans and period doubling bifurcations. In *IEEE Computers in Cardiology.* IEEE Computer Society, Silver Spring, 1984, pp. 167-170.
4. Glass L, Mackey M. *From Clocks to Chaos. The Rhythms of Life.* Princeton University Press, Princeton, 1988.
5. Chialvo DR, Gilmour RF, Jalife J: Low dimensional chaos in cardiac tissues. Nature 1990;343:653-657.
6. Vinet A, Chialvo DR, Michaels D, et al: Nonlinear dynamics of rate-dependent activation in models of single cardiac cells. Circ Res 1990;67:1510-1524.
7. Guevara MR, Alonso F, Jeandupeux D, et al: Alternans in periodically stimulated isolated ventricular myocytes: Experiment and model. In Goldbeter A, ed. *Cell to Cell Signaling: From Experiments to Theoretical Models.* Academic, London, 1989, pp. 551-563.
8. Lewis TJ, Guevara MR: Chaotic dynamics in an ionic model of the propagated cardiac action potential. J Theor Biol 1990;146:407-432.
9. Chialvo DR, Michaels D, Jalife J. Supernormal excitability as a mechanism of chaotic dynamics of activation in cardiac Purkinje fibers. Circ Res 1990;66:525-545.
10. Chialvo DR, Jalife J: On the nonlinear equilibrium of the heart. Locking phenomena and chaos in cardiac Purkinje fibers. In Zipes DP, Jalife J, eds. *Cardiac Electrophysiology: From Cell to Bedside.* WB Saunders, Philadelphia, 1990, pp. 204-214.
11. Jalife J, ed. Mathematical approaches to cardiac arrhythmias. Ann NY Acad Sci 1990;591.
12. Vinet A, Leon LJ: Circulation of activity in a loop of model myocardial cells. Proceeding of the 13th IEEE\EMBS Conference, Orlando, Florida, 1991, pp. 508-509.
13. Vinet A, Roberge FA: The dynamics of sustained re-

entry in a ring model of cardiac tissue. Ann Biomed Eng 1994;22:568-591.
14. Ito H, Glass L: Theory of reentrant excitation in a ring of cardiac tissue. Physica 1992;56D:841-846.
15. Courtemanche M, Glass L, Keener JP: Instabilities of a propagating pulse in a ring of excitable media. Phys Rev Lett 1993;70:2182-2185.
16. Chialvo DR: NIH Grant Application 1R29 HL47484-01: Modeling of reentrant cardiac rhythms and ventricular fibrillation. 1989 (download from Web site *www.santafe.edu/~dchialvo/proposal.htm*).
17. Davidenko J, Kent P, Chialvo DR, et al: Sustained vortex-like waves in normal isolated ventricular muscle. Proc Natl Acad Sci USA 1990;87:8785-8789.
18. Koller ML, Riccio ML, Gilmour RF Jr: Dynamic restitution of action potential duration during electrical alternans and ventricular fibrillation. Am J Physiol 1998;44:H1635-H1642.
19. Riccio ML, Koller ML, Gilmour RF Jr: Electrical restitution and spatiotemporal organization during ventricular fibrillation. Circ Res 1999;84:955-963.
20. Winfree AT: Evolving perspectives during 12 years of electrical turbulence. Focus issue: Fibrillation in normal ventricular myocardium. Chaos 1998;8:1-19.



Belfry and bell tower, Kremlin, Moscow.