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Is there chaos in cardiology?

A recent paper stated that "the health care system in the United States is in chaos."¹ Though I am sure readers know what was meant, we have to be careful these days about the definition of chaos. Consulting a medical dictionary is unhelpful because there, chaos (*Pelomyxa carolinensis*) is an amoeba.² Descriptions in Webster³ ("a state of things in which chance is supreme . . . nature that is subject to no law . . . a state of utter confusion completely wanting in order, sequence, organisation or predictable operation") do not quite cover the modern, mathematical redefinition of chaos.

The new chaos is characterised by deterministic behaviour, where irregular patterns obey mathematical equations and are critically dependent on initial conditions.⁴ Modern chaos theory has been applied to a wide variety of biological phenomena⁵ and has become quite fashionable. In certain circles you are regarded as a barbarian if your conversation is not garnished with terms such as Hopf bifurcation points, Liapunov numbers, phase locking, or fractals.

Chaos theory has been used in two areas of cardiac electrophysiology: (a) the behaviour of cardiac tissue, or isolated myocytes, during repetitive stimulation and (b) fibrillation and prefibrillatory states.

Chaos is irregular behaviour occurring in a nonlinear dynamic system. Cardiac cells may have several nonlinear, time-dependent variables (for instance supernormal excitability) and may exhibit irregular response patterns at a certain stimulation frequency.^{6,7} When isolated sheep Purkinje fibres exposed to a solution containing 7 mmol/l K⁺ are repetitively stimulated at progressively faster rates, the so-called devil's staircase is seen, where 1:1 responses change into 2:1 and 3:1, with intermediate Wenckebach periodicity between the 1:1 and 2:1, and 2:1 and 3:1 responses. No irregular activity occurs. When, however, the extracellular K⁺ concentration is lowered to 4 mmol/l, and the fibres exhibit a brief period of supernormal excitability during the repolarisation phase, deterministic

chaotic behaviour occurs at certain cycle lengths: either the stimulus-response pattern shows complex irregularities where no sequence is ever repeated in exactly the same way (this occurs at cycle lengths around 200 ms), or at cycle lengths of 50 ms the relation between cycle length and action potential amplitude is chaotic.⁷ This example is chosen to show, on the one hand, that chaotic behaviour can indeed be induced in cardiac tissue, and that some satisfaction can be derived from the consideration that a unifying concept, chaos theory, links the stimulus-response patterns in cardiac cells with other phenomena such as growth during embryonic development⁸ or the activity of phrenic nerves during mechanical ventilation of anaesthetised, paralysed cats.⁵ On the other hand, the conditions in which chaotic activity arises are extreme: artificial stimulation of isolated tissue at a certain K⁺ concentration at unphysiological frequencies.

Can chaotic behaviour be detected in "naturally" occurring rhythms? The obvious candidate for study is ventricular fibrillation, which traditionally has been called chaotic in the Webster sense. The identification of chaos in an existing rhythm is difficult. One technique is power spectrum analysis. A broad-band power spectrum is associated with chaos; however, ordinary random noise has a broad power spectrum as well. The power spectrum of electrocardiographic recordings during ventricular fibrillation is narrow^{9,10} and Kaplan and Cohen concluded from their analysis that "there is little utility in classifying fibrillation as chaotic."¹⁰ Would it be useful if fibrillation, or any other rhythm or conduction disorder, could be classified as chaotic? In this respect, the investigators in the chaotic domain are very enthusiastic: "A finding that ventricular fibrillation is chaos would suggest that there is a single mechanism at work in VF, and would provide guidance in the search for clinical precursors of VF";¹⁰ "... such new theories may help to strengthen the ties between the basic scientist and the cardiologist by opening new research avenues which may lead to the disclosure of the fundamental mechanisms of severe cardiac arrhythmias

and sudden death”;⁷ “The application of nonlinear systems theory to electrophysiology . . . may have clinical implications.”⁷ In a recent paper, describing a relation between T wave alternans in dogs with acute coronary artery occlusion and subsequent fibrillation, it was claimed that “a new approach is provided for quantification of susceptibility to malignant arrhythmia” and that “T wave alternans may represent a prechaotic state because bifurcate behaviour is the hallmark of chaos.”¹¹

These quotes indicate that a great deal is expected from studies applying chaos theory to cardiac rhythms: more insight into arrhythmogenic mechanisms and the identification of individuals at high risk for sudden cardiac death. It is here that I have my doubts. Certainly, new avenues should be explored, and possibly “we are sure to see dramatic advances in the field”¹² if we use nonlinear dynamics as a tool to study complex cardiac rhythms. In my view, however, cardiac arrhythmias ultimately have to be understood in terms of cardiac electrophysiology, and are due to changes in variables such as conduction velocity, excitability, automaticity, afterdepolarisations, electrotonic interactions between areas in the heart with different electrical properties, which in their turn are due to changes in properties of ionic channels, pumps, and receptors in cellular and subcellular membranes. Is my understanding that T wave alternans may be a harbinger of ventricular fibrillation in acute ischaemia improved because it is a prechaotic state (presumably leading to “chaotic” fibrillation where chaos is used in the old sense and not in the modern one) or because it marks the development of post-repolarisation refractoriness which sets the stage for unidirectional block, one of the prerequisites for re-entry?^{13 14}

In my opinion our insight into arrhythmogenesis will be advanced by the application of chaos theory only if the link

between “modern” chaos theory and “old fashioned” electrophysiology is established. Here, a mathematician who can model iterative non-linear systems and who understands the language of the cardiac electrophysiologist and of the practicing cardiologist may be of help.

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