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Chaos – No Randomness in Cardiac Physiology

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Key Words

Fractals · Organ perfusion · Heterogeneity · Mathematics in medicine

In 1994, on our way back from Luzern, waiting for a flight from Zürich's airport I kept hacking on my pocket calculator and Professor Konrad Messmer – startled – asked what I was doing. I did not hesitate to explain and ask for his permission to follow my plans to do a series of measurements in an investigation already under way. Of course, this included my asking him for funding. 'Go ahead' was his answer without further questions. This open, interested approach to every new possibility, every problem posed is typical for Professor Konrad Messmer. This started me off on a successful pursuit of questions about non-linear phenomena in physiology. One of the more general questions I will lay out in the following.

Not so many years ago, heterogeneity of cardiac perfusion was thought to be a sign of coronary artery disease. In reality, heterogeneity of organ perfusion is a necessary adaptation to heterogeneous metabolism and has nothing to do with disease. This knowledge has led to the desire to adequately measure perfusion heterogeneity. But such a measurement is far from trivial since results depend on the resolution of measurement. The higher the resolution, the larger heterogeneity will appear. In 1989, Bassingthwaighte demonstrated that dependence of measured perfusion heterogeneity of resolution follows a non-linear law [1]. The coronary vascular tree has a complex structure the description of which is not possible with the means of general Euklidian geometry. If, however, Mandelbrot's fractal geometry is applied, the coronary vessel tree lends itself to classification as a self-similar, recursively constructed object [2]. Fractal geometry of the coronary vascular tree and – in analogy – fractal geometry of heterogeneity of myocardial perfusion is standard knowledge. Interestingly, fractals are considered a typical expression of deterministic chaos as known in modern physics [3]. The question forming the basis for the hypothesis driving our research was whether fractal geometry is an expression of deterministic chaos also in the case of myocardial perfusion. In a series of projects we looked for signs of deterministic chaos in heterogeneity of cardiac perfusion. This question seemed to be relevant since other signals in cardiac physiology display chaotic variability. The application of modern chaos theory has led to eminent advances in the understanding of regulation of cardiac signals: reduction of chaotic heart rate variability has been shown to precede serious cardiac dysrhythmias and to imply reduced life expectancy.

In general language use, chaos is defined as 'utter confusion and disorder' (MacMillan Contemporary Dictionary). Modern physics, however, does not consider chaos to be confusion without rules. Chaos occurs in dynamic systems that react sensitively to very small changes of starting conditions. Thus, minimal changes of these con-

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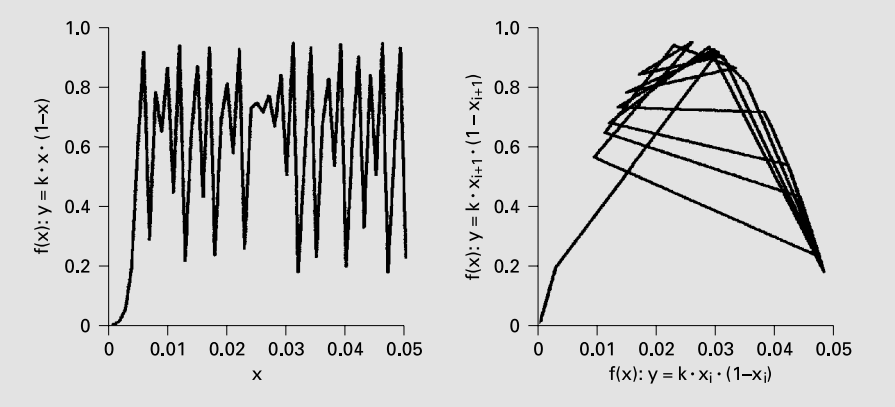


Fig. 1. Example for a method to graphically detect chaos. Left panel: linear representation of the function f(x): $y = k \cdot x \cdot (1 - x)$, with k = 3.8. The result of the equation is repeatedly inserted as x in the next calculation (logistic map). The graph of the function is non-periodic, i.e. there are no repetitions. There is no random element in the equation, i.e. it is completely pre-determined. The function is chaotic. Right panel: processes with unknown underlying functions can be graphically examined using special representations. The 'return map is shown here. The abscissa shows a value of the function at a certain point. The result of the function is used to repeatedly calculate a result which is then shown on the ordinate. Results of one function are alternatingly displayed on the abscissa and the ordinate. This graphical representation can give hints whether a function is chaotic (as in this example) or whether there is periodicity, i.e. whether function values are exactly repeated excluding chaos.

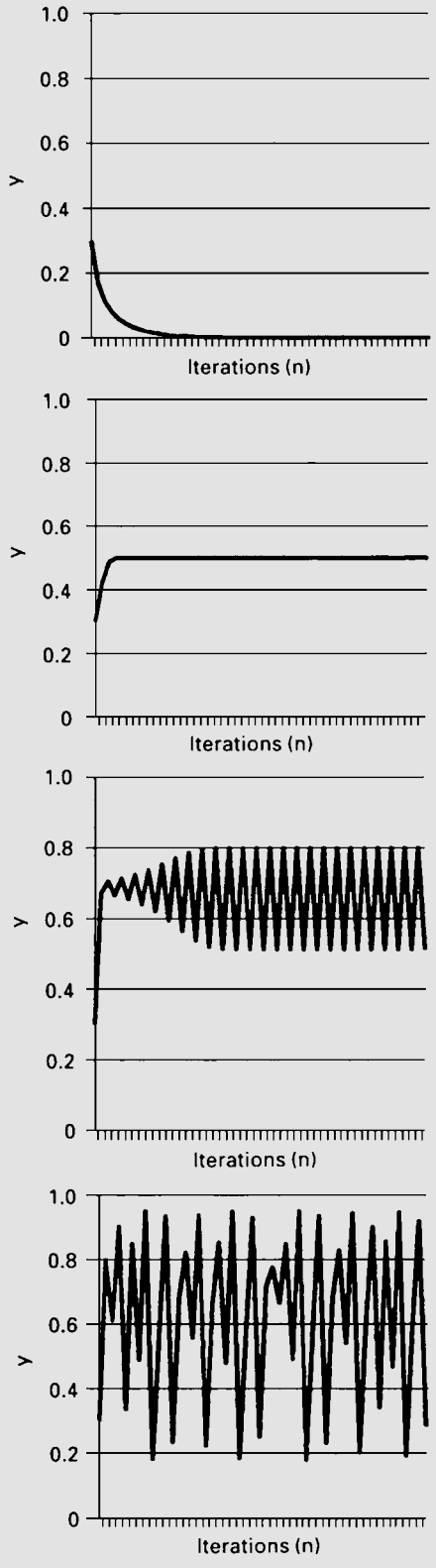
ditions lead to great variation of results. Chaos theory was not knowingly founded by E. Lorenz in the sixties of the last century during his attempts to simulate atmospheric flow with differential equations. Figure 1 shows a a simple example of chaos. The quadratic equation

$$y = k \cdot x \cdot (1 - x) \quad (1)$$

defines an ordinary parable. This equation is often referred to as 'logistic map'. y can be calculated with a set value for k and an arbitrary x. The result, say y_1, is taken as x for a repeated calculation using the same equation – one gets y_2. This is done a great number of times, e.g. until y_{1000} or, generally, y_n. Much like a microphone placed to close to the speaker this mathematical coupling leads to a loss of order. However, whether chaos or order occurs depends on the parameter k in the equation. Figure 2 shows a part of the process that is described by equation 1. Doing the series of calculations with equation 1 with the parameter k set below 1 leads to a continuous series of zeros as results (upper panel in fig. 2). If, however, k is set between 1 and 3, the results swing about one single value that is eventually reached and kept (second panel in fig. 2). If k is greater than 3, stability disappears. If k equals 3.2, there are two end-points that eq. 1 alternately reaches (third panel in fig. 2). Letting k become greater results in sudden doubling of the number of end-points of eq 1. Sequentially, 4, 8, 16, 32, ... results can be observed. If k is larger than approximately 3.57, there is a virtually unlimited number of 'end-points (or no end-point). No periodicity of sequential results of eq. 1 can be discerned (lower panel of fig. 2). The results of a series of calculations using the logistic map appear random – 'chaotic' – but it is not! Everything is pre-determined with a simple equation.The logistic map is far from being a mere mathematical game. The logistic map is used by biologists to understand the kinetics of seemingly random variations of populations. Epidemiologists are enabled to understand appearing and disappearing of epidemics. The logistic equation is of central importance for chaos theory. Using this equation, M.J. Feigenbaum at the Los Alamos National Laboratory found a general structure in chaos, hidden in the logistic map and in natural processes: the interval of the parameter k in eq 1 that leads to one end-point of a series of calculations is approximately 4.669 times as large as the interval that leads to two end-points. This interval, in turn, is 4.669 times as large the interval that leads to four end-points, and so forth.

In contrast to general language use, chaos displays the following properties: (1) unpredictability (no randomness); (2) lack of periodicity; (3) limited range of possible results; (4) non-periodic order (hidden structure); (5) sensitive dependence on starting conditions.

We investigated regional myocardial perfusion in 28 anesthetized pigs. For measureing regional blood flow we



injected radioactive microparticles (15 μm diameter) that embolize in small arterioles. In 23 animals we induced a hemorrhagic shock and after 60 min resusciated with different therapeutic regimens [5, 6]. Five animals did not suffer from shock and were observed for hours to guarantee stability of the animal model. For this paper, we report excerpts of the measurements under control conditions. After completion of the experiments, hearts were excised and the left ventricle was dissected into 102–204 specimens. Regional perfusion was measured by quantifying emitted radioactivity.

For appreciation of chaos in perfusion we developed methodology that is based on graphically detecting aperiodic order that is not directly apparent in a chaotic signal. Briefly, this is based on transforming the signal into a presentation with a different geometric dimension. For example, the time-dependent variation of a variable may be displayed as an irregular curve in a Cartesian coordinate system with time on the abscissa. For detection of chaos one transforms this one-dimensional signal into a two-dimensional representation with consecutive data pints given alternately on the ordinate and the abscissa, respectively. An exemplary application of such a transformation is given in figure 1, right panel. Ordinary methods for examining chaotic dynamics are not applicable for three-dimensional data sets that result from measuring three-dimensional processes such as spatial distribution of regional myocardial perfusion. New ways had to be found.

Following the criteria given above, chaos in myocardial perfusion may be suspected since regional myocardial perfusion is not predictable. This was shown by many studies. Still, blood flow is not random, since heterogeneity of perfusion follows substrate needs of the myocardium. Repetitions of certain patterns of perfusion – periodicity – could not be found in our data. This has been confirmed by other authors. The possible intervals of values of left ventricular perfusion is limited, variations from 25 to 200% of the average value occur. These criteria have

Fig. 2. Different graphical representation of the equation $y = k \cdot x \cdot (1 - x)$ depending on the parameter k. The abscissae show the number of iterations used. The ordinate gives the function value. Upper panel: k is 0.8. After few iterations (almost) 0 is reached as an end-point. Second panel: k is 2. The function value quickly becomes 0.5 an does not change anymore. Third panel: k is 3.2. The function value varies between two values: ~0.51 and ~0.8. A so called bifurcation has occurred. The number of function end-points has doubled. As k is increased, many more bifurcations occur. Lower panel: k is 3.8. An unlimited number of 'end-points' (or no end-point at all) is reached and there is no periodicity. No value is ever repeated exactly.

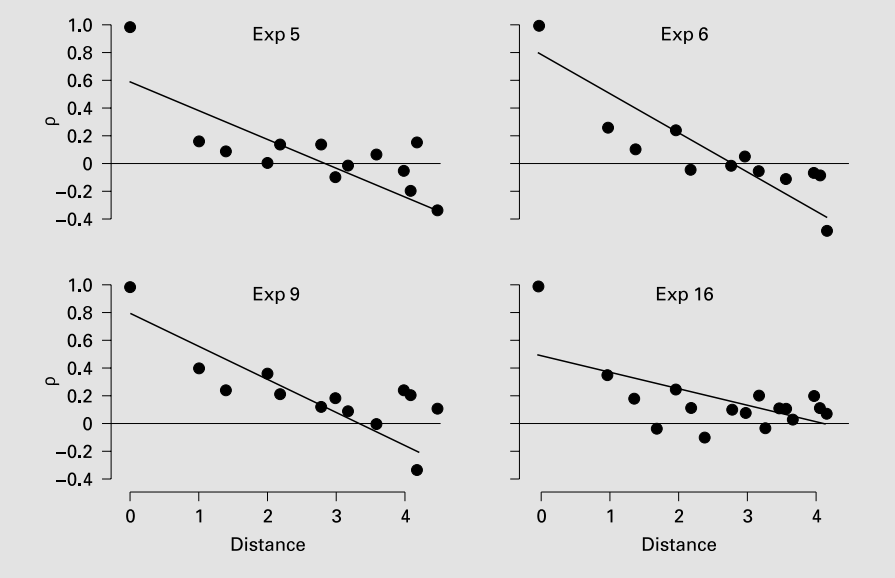


Fig. 3. Distance dependent correlation of regional myocardial perfusion. The x-axis shows the spatial distance between myocardial specimens in arbitrary units. The y-axis gives the correlation coefficient (rho). The four panels represent results of four typical experiments (codes 5, 6, 9, and 16). In all experiments the typical distance-dependent pattern of correlation was observed. We interpret this order as the hidden pattern in the seemingly un-ordered distribution of perfusion. This is evidence for chaos in regional myocardial blood flow.

been observed before. A method to detect aperiodic order of regional myocardial blood flow and proof for sensitive dependence on initial conditions are lacking as yet. Heterogeneity of blood flow is determined by fractal geometric architecture of the coronary vascular tree. It follows that a certain order must be given. This order is the similarity of perfusion values depending on the number of coronary vascular bifurcations occurring between feeding vessels of myocardial samples. This order supports the assumption of chaos in perfusion but is hidden by the inhomogeneity of the dichotomous separation of blood flow at each of numerous vascular bifurcations.

Spatially separated organ regions are perfused by arterioles fed by larger vessels that have been separated by one of the first bifurcations in the vascular tree. Perfusion of spatially neighboring samples stems from arterioles that have been separated in one of the later generations of the vascular tree. The influence of spatial distance between myocardial samples on linear correlation (= self-similarity) of perfusion can be quantified with spatial correlation. To this end, a modified version of the linear correlation coefficient (Pearson's product moment correlation coefficient) is used. Spatial correlation is a one-dimensional parameter of three-dimensionally distributed regional perfusion. As described, to detect chaos a transformation from one to a higher dimension should be attempted. By calculating correlation (1. dimension) for all possible distances between paired myocardial samples and plotting it against distance (2. dimension) a repeating pattern is obvious (fig. 3). In this order, we see proof for

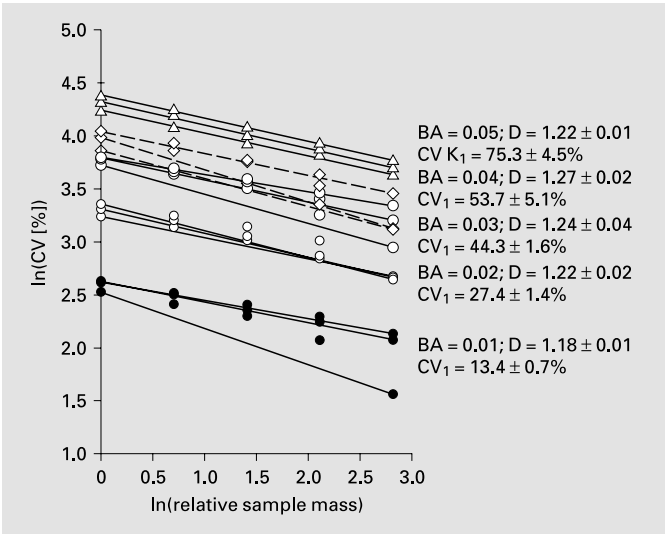


Fig. 4. Examination of sensitive dependence of heterogeneity of myocardial perfusion on initial conditions. Distribution of organ perfusion was simulated using a computer model. The initial condition to be varied was asymmetry of distribution of perfusion at vascular bifurcations (BA). The coefficient of variation (CV) was calculated for different (simulated) resolutions of measurement. From the regression of the coefficients of variation of one data set at different resolutions, the fractal dimension (D) can be calculated. One set of symbols with corresponding regression line belongs to one run of the model. The x-axis shows the natural logarithm (ln) of simulated sample mass as a measure of resolution of measurement. The y-axis shows the natural logarithm of coefficient of variation. In this logarithmic representation, the coefficient of variation linearly depends on resolution. The coefficient of resolution increases very strongly with increasing resolution. This demonstrates sensitive dependence on initial conditions.

non-random order and an evidence for chaos in myocardial perfusion.

Experimental proof of sensitive dependence on initial conditions of myocardial perfusion is impossible due to a vast number of confounding variables. Therefore, we approached the problem theoretically using a computer model. Using this model, we investigated the effect of minimal changes of blood flow distribution at coronary bifurcations on heterogeneity of myocardial perfusion. Our hypothesis was that minimal asymmetry of blood flow distribution would lead to strong heterogeneity, i.e. sensitive dependence on initial conditions as postulated by the assumption of chaos in myocardial perfusion. The simulation produced uniform blood flow distribution if it was run without asymmetry of distribution (1 ml/min in each of 256 myocardial samples). We performed three simulations for each of five asymmetry conditions. Each coronary bifurcation was assigned a normally distributed, random asymmetry. The mean value of the normal distribution was 0 (symmetry). The standard deviation was a parameter of the model and varied from 0.01 to 0.05 in steps of 0.01.

The results from these simulations were strongly heterogeneous distributions. Figure 4 shows coefficients of variation and fractal dimensions of simulated data sets. Change of asymmetry did not influence fractal dimension D. D of simulated blood flow was between 1.18 ± 0.01 (asymmetry: 0.01) and 1.27 ± 0.02 (asymmetry: 0.04). In contrast, the coefficient of variation rose strongly from 13.4 ± 0.7% to 75.3 ± 4.5% if asymmetry was increased from 1% (0.01) to 5% (0.05). We interpret strongly increasing heterogeneity of simulated perfusion in response to tiny changes of bifurcation asymmetry as sensitive dependence of simulated myocardial perfusion on initial conditions.

In conclusion, we have shown that heterogeneity of myocardial perfusion is chaotic. Non-periodicity, heterogeneity, sensitive dependence on initial conditions, and hidden order are properties of chaos that can be found in distribution of myocardial perfusion.

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