Aging and the complexity of cardiovascular dynamics

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ABSTRACT Biomedical signals often vary in a complex and irregular manner. Analysis of variability in such signals generally does not address directly their complexity, and so may miss potentially useful information. We analyze the complexity of heart rate and beat-to-beat blood pressure using two methods motivated by nonlinear dynamics (chaos theory). A comparison of a group of healthy elderly subjects with healthy young adults indicates that the complexity of cardiovascular dynamics is reduced with aging. This suggests that complexity of variability may be a useful physiological marker.

INTRODUCTION

Normal human aging is associated with a progressive impairment in several physiologic control systems that interact to maintain cardiovascular homeostasis. Variability in heart rate and blood pressure has been used to study the function of the cardiovascular control system (1–12). Recently, a general qualitative hypothesis of variability and pathology has been proposed; the dynamics of the healthy physiological control system produce an apparently irregular and highly complex type of variability, whereas disease or aging is often associated with more regularity and less complexity (13, 14). Chaos theory provides two methods of quantifying complexity-entropy and dimension- that can be modified to make them applicable to systems that may not fit into the deterministic framework of chaos, i.e., systems that are genuinely random or that are of such high order that they cannot be adequately described from available lengths of data.

In the study reported here, continuous, noninvasive blood pressure and heart rate were analyzed in 16 healthy young adults and 18 healthy elderly subjects. We found that the older subjects had a lower complexity in both heart rate and blood pressure, despite a larger blood pressure variance. The results support the proposition that increased regularity is associated with aging, and show that complexity can be measured in a consistent way between individuals.

We collected beat-to-beat systolic blood pressure and heart rate signals from healthy adults in two groups: young (age 21–35, mean 28) and elderly (age 62–90, mean 75), none of whom was taking cardioactive drugs. Each subject was studied in three different conditions. First, while lying in a supine position on a tilt-table, the subjects breathed along with a metronome signal (0.25 Hz), regulating tidal volume themselves. Next, while remaining supine, the subjects breathed quietly in a spontaneous rhythm. Finally, the subjects were inclined to a 60° head up position and continued to breathe quietly in a spontaneous rhythm. These three conditions will be called metronome, quiet, and tilt, respectively.

The heart rate signal was derived from one channel of a digitized electrocardiogram (ECG). Continuous blood pressure was measured noninvasively by use of arterial tonometry applied to the radial artery (15) (CBM 3000; Colin Electronics; Komaki-City, Aichi, Japan). Both the ECG and continuous blood pressure signals were sampled at 250 Hz and digitized with 12-bits resolution. A tachometer (16) was used to generate heart rate and systolic blood pressure signals sampled at 5 Hz. Care was taken to minimize the influence of cardiac ectopy on the heart rate signal.

For each subject, the mean, standard deviation, and power spectrum of heart rate and systolic blood pressure were calculated using a 409-s long segment of data. (See Table 1.) Mean heart rate is similar for old and young, but the variance is lower for old compared to young (4, 17). Systolic blood pressure is higher in the old group, and the variance of systolic blood pressure is also somewhat higher in old compared to young (18).

The shapes of the power spectra of heart rate and blood pressure also show differences between old and young. Most notable is the amount of respiratory variation in heart rate: when supine, young people have considerably more respiratory variability than old, although this difference largely disappears upon tilting. This change probably reflects reductions in parasympathetic control of heart rate during tilt, which are proportionally greater in young than old (3, 17).

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0006-3495/91/04/945/05 $2.00

TABLE 1 **Group characteristics of heart rate and blood pressure**

	Metronome		Quiet		Tilt	
	old	young	old	young	old	young
			Heart Rate (*bpm*)			
mean	63.2 (8.9)	61.0 (6.4)	60.9 (8.0)	61.1 (6.5)	69.8 (11.0)*	77.8 (9.2)
SD	2.1 (1.0)*	3.4 (1.0)	2.8 (0.8)*	4.1 (1.0)*	3.0 (1.0)*	5.5 (1.8)
resp. var. (%)	22.4 (12.4)*	40.6 (13.2)	13.8 (8.2)*	30.1 (13.0)	12.9 (9.0)	16.3 (8.4)
			Systolic Blood Pressure (mmHg)			
mean	127 (12)*	117 (17)	132 (21)*	109 (14)	128 (20)	108 (15)
SD	4.3 (2.3)	3.9 (2.5)	5.6 (3.8)*	3.2 (1.3)	6.6 (3.1)*	5.0 (2.7)
resp. var. (%)	14.3 (9.7)	17.7 (14.8)	8.3 (6.2)	12.2 (5.8)	9.2 (4.3)*	17.8 (7.4)

The mean, standard deviation (SD) (that is, the square root of variance), and percentage of total variance in a respiratory band (resp. var.) (0.1 to 0.3 Hz) for the heart rate and blood pressure signals. Shown are the means of these measures for each group with the group SD of the measure in parentheses. *Indicates that the difference between the old group ($n = 18$) and young group ($n = 16$) is significant at the $p < 0.02$ level using a two-tailed Student's t-test.

Although differences between old and young are clearly reflected by these measures of variability in heart rate and blood pressure, they do not directly address the complexity of the heart rate and blood pressure signals. Complexity is a different concept than the amount of variability as might be measured by the variance of a signal. For example, two sine waves of different amplitudes might be thought of as equally complex, although their variances are different.

The theory of chaos can provide a meaningful definition of complexity and means of quantifying it. One way to measure complexity is via the dimension of the dynamical system needed to express the signal. For a deterministic system the dimension is often interpreted as the number of dynamic variables in the difference or differential equations needed to construct a dynamical system that will reproduce the measured signal, although this interpretation is sometimes problematic.[1] From this perspective, a random signal is maximally complex, with infinite dimension for an infinitely long signal. A periodic system has dimension one. Another way to quantify complexity is by entropy, which deals with the amount of information needed to predict the future state of the system. Again, more complex dynamics are represented as a larger entropy, and random noise is maximally complex (19). (For an alternative perspective, see reference 20a,b and 21.)

Numerical methods exist that allow the dimension and entropy to be estimated from a time series (22–24). These algorithms require that signals be measured for long periods without any change in the parameters of the system under study. Such signals may not be available for physiological systems.

[1]For a system measured after transients have died out, that is, a system whose trajectory is on an attractor, the dynamical variables related to transients will not be represented in the dimension.

We have modified the correlation dimension and Kolmogorov entropy algorithms to generate statistics that appear to be usable with hundreds of seconds of heart rate and blood pressure data. These statistics, the "approximate dimension" and "approximate entropy," lose the property to demonstrate deterministic chaos, but retain an ability to distinguish data sets by a measure of complexity. The algorithms can also be applied to distinguish classes of stochastic processes from one another. The values obtained from the algorithms should not be interpreted as estimates of the correlation dimension or Kolmogorov entropy of the system, but as a distinct measure of complexity.

Both the approximate entropy and dimension are derived from the correlation integral $C_i^m(r)$ which is the number of points in the signal closer than distance r to the ith point when embedded in an m-dimensional space. A family of approximate entropy statistics is defined by $ApEn(m, r) \equiv \Phi^m(r) - \Phi^{m+1}(r)$, where

$$\Phi^m(r) \equiv \sum_{i=1}^{N-m+1} \frac{\ln C_i^m(r)}{N - m + 1}.$$

Based on theoretical calculations and a study of neonatal heart rate (25) for data sets of 1,000 beats, the choice of $m = 2$, $r = 0.2$ times the signal's standard deviation, and an embedding lag of approximately one beat (0.8 s) appears to produce a useful *ApEn* statistic. These input parameters were employed in the results reported here.

The approximate dimension is defined as

$$\upsilon \equiv \frac{\ln C(r_b) - \ln C(r_a)}{\ln r_b - \ln r_a},$$

where $C(r) = \Sigma_{i=1}^{N-9} C_i^{10}(r)$. Any two points in the embedded signal are separated by some distance; we can speak of a "distance between a pair of points." $C(r)$

describes the distribution of distances r between the $\sim N(N-1)/2$ pairs of points in the embedded signal. r_a is selected as the distance r that only 0.5% of the pairs of points are closer than. Similarly, r_b is the distance that only 75% of the pairs of points are closer than. This means $C(r_a) \equiv 0.005$ and $C(r_b) \equiv 0.75$. Thus, υ reflects the slope of the correlation integral over the lower $\approx 3/4$ of its vertical scale. The purpose of selecting r_a and r_b in this way is to minimze the effects of external noise in the signal (noise often manifests itself at small length scales), and to make the calculations robust to outliers in the measured signals that would distort the largest length scales.

For the present study, using one of the studied signals as an exemplar, we set the embedding dimension to $m = 10$ with a lag window length of 29 s. For reference, the characteristic time scale of respiratory variability in heart rate and blood pressure is typically 4–5 s. The time scale for sympathetic and thermoregulatory variability is typically 10–20 s (26).

These methods of calculating the approximate dimension and entropy are independent of the mean and variance of the signal, and allow the same range of dynamical length scales to be considered for all the signals analyzed. The dimension is often calculated by others by looking at the slope of the most linear segments of the correlation integral (27–29). These techniques involve a means of evaluating a "score" for each plausible linear segment of the correlation integral (e.g., the score might be based on the length of the linear segment and the goodness of fit to a line). The "best" linear segment is chosen. Whereas these techniques emphasize the possible existence of strange attractors, the length scale chosen can depend discontinuously on the signal because a small change in the signal can change the relative ranks of the candidate linear segments and thereby change the calculated dimension substantially. Because our technique does not examine the linear scaling of the correlation integral, it is improper to interpret the dimension we calculated as the dimension of an attractor. Similarly, it would be incorrect to infer from our analysis of dimension that an attractor necessarily exists.

The approximate dimension was lower for the old group than for the young for both blood pressure and heart rate for each of the conditions. (See Table 2.) In four of the six categories, this difference is significant at the $p < 0.02$ level. A similar result holds for the approximate entropy of the signals: the old group has a smaller mean entropy than the young group. A scatter plot of the calculated dimensions and entropies for heart rate and blood pressure during quiet breathing indicates that the difference between the old and young groups is not the result of a few outlying individuals but is representative of the group as a whole. (See Fig. 1.)

TABLE 2 **Group means (SD) of the approximate entropy and dimension of the heart rate and blood pressure signals**

		Dimension		Entropy	
state	signal	old	young	old	young
metro	h	3.82 (0.41)*	4.33 (0.31)	0.88 (0.07)*	0.94 (0.04)
	bp	3.39 (0.71)	3.70 (0.73)	0.78 (0.14)	0.81 (0.12)
quiet	h	3.41 (0.57)*	4.20 (0.53)	0.79 (0.12)*	0.90 (0.04)
	bp	3.12 (0.61)*	3.61 (0.46)	0.69 (0.15)*	0.81 (0.10)
tilt	h	3.69 (0.70)	3.88 (0.42)	0.84 (0.13)	0.81 (0.07)
	bp	3.23 (0.73)*	3.94 (0.43)	0.73 (0.15)*	0.86 (0.06)

*Reports statistical significance; see the caption for Table 1.

To what extent do these differences in complexity simply restate already known differences in heart rate and blood pressure variability between old and young? The approximate dimensions and approximate entropies were calculated in a manner that makes them completely independent of the mean and variance of the signal. This independence of the dimension and entropy from the variance is highlighted by the fact that both entropy and dimension are lower for the old group than for the young for both heart rate and blood pressure, whereas the variance of the old group was less than that of the young group for heart rate and greater for blood pressure.

To investigate the role that differences in the respiratory component of heart rate and blood pressure play in the approximate dimension and entropy, we repeated the calculations on the heart rate and blood pressure signals after digitally filtering them to pass only their respiratory-band (0.1–0.3 Hz) components. For blood pressure and heart rate, for all three conditions, the

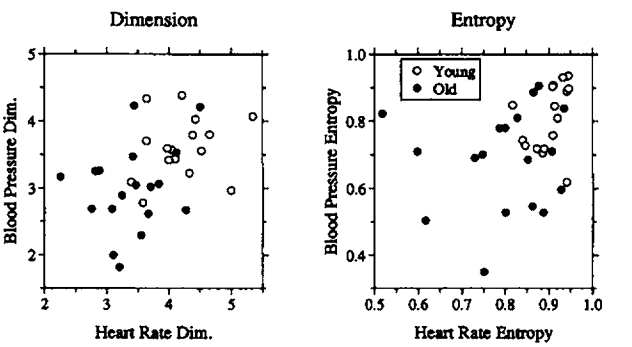

FIGURE 1 A scatter-plot of the approximate dimension and entropy for each of the subjects during quiet breathing. Each subject is represented once in each of the two graphs.

dimension and entropy were lower for the old group than the young. In four of the six categories, this difference was significant at the $p < 0.02$ level. The dimensions and entropies of the respiratory-band signals were in every case less for metronome breathing than for quiet breathing or tilt. This corresponds to the intuitive notion that breathing to a metronome should produce simpler patterns than spontaneous breathing.

Because all subjects were either supine or tilted, it does not appear that the lower complexity for the old group can be ascribed to different activity levels of the two groups. As the differences in complexity between old and young were similar for metronome and quiet breathing, simple differences in breathing patterns do not account for the results, which appear to reflect genuine changes with aging in the physiological control of the cardiovascular system.

This work was supported by grants to Lewis A. Lipsitz from the Hebrew Rehabilitation Center for Aged and the National Institute on Aging Teaching Nursing Home Award (AG04390), to Mark I. Furman from the Eunice and Julian Cohen Medical Education Fund at the Brigham and Women's Hospital, and to Ary L. Goldberger from the G. Harold and Leila Y. Mathers Charitable Foundation, the National Heart, Lung and Blood Institute (III,42172), Colin Electronics Ltd., and the National Aeronautics and Space Administration (NAG-2-514).

Received for publication 27 August 1990 and in final form 17 December 1990.

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