Physiology and Pharmacology
Physiol Pharmacol 21 (2017) 260-265
www.phypha.ir/ppj

Short Communication

# The controllability of cardiac rhythm in elderly

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## Abstract

**Introduction:** Recent reports have shown that rare fluctuations in cardiac cycles are 'forgotten' quickly in healthy individuals and it is possible to quantify the "memory length" of a physiological time-series using an inverse statistical approach.

**Methods:** In the present study, we assessed the effect of aging on memory length in cardiac rhythm.

**Results:** There was a longer memory length in cardiac time-series of elderly subjects in comparison with younger adults for both decelerating and accelerating rare fluctuations in cardiac rhythm.

**Conclusion:** The increased memory length of the cardiac time-series in elderly subjects may indicate reduced controllability of cardiovascular regulatory system.

**Keywords:**
Heart rate variability;
Memory length;
Controllability;
Elderly
**Received:** 8 Aug 2017
**Accepted:** 16 Nov 2017

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## Introduction

Healthy heart rhythm is complex and shows a great degree of variability and fluctuation in a wide range of time scales. This phenomenon is referred to as heart rate variability (HRV) and is reflected by interaction of various events such as neuroendocrine and autonomic nervous system as well as the intrinsic variability of cardiac pacemaker.

Over the last three decades, many linear (eg. SDNN) and nonlinear (eg. entropy) methods have been described for quantification of patterns that are embedded in heart rate fluctuations (Buchman, 2002; Buchman, 2004; Glass et al., 1986; Glass et al., 1990; Glass et al., 2002a; Glass et al., 2002b; Goldberger, 2001; Guevara et al., 1981; Ivanov et al., 1996). Although these computational methods have been demonstrated to have both diagnostic and prognostic values in a variety of diseases (Ahmad et al., 2009; Mani et al., 2009; Moss et al., 2014), their physiological interpretation is not well characterized. For instance, Goldberger and colleagues have extensively studied the effect of aging as well as heart failure on fractal-like temporal structures in cardiac time-series; however, the physiological basis of fractal dynamics in cardiorespiratory rhythm has not fully been elucidated (Goldberger et al., 2002b).

We have recently employed inverse statistical analysis in order to quantify "memory" in physiological time-series (Ebadi et al., 2011; Shirazi et al., 2013; Mazloom et al., 2014). In a cardiac time-series, "memory length" can be quantified by determining the time scale over which rare fluctuations do not appear randomly (Ebadi et al., 2011; Shirazi et al., 2013). Previous reports have provided evidence to show that rare fluctuations in cardiac cycles are 'forgotten' quickly in healthy subjects while their memory is kept

for longer in pathological conditions such as heart failure and systemic inflammation (Mazloom et al., 2014; Shirazi et al., 2013). According to control theory, a larger “memory length” makes it harder to control the system. Therefore, an advantage of calculating the memory length is that it can be used as an indirect measure of “controllability” of the cardiovascular regulatory system (Mazloom et al., 2014). Controllability has a physiological interpretation since autonomic regulation of cardiac output needs a high degree of controllability in order to cope rapidly with ever-changing environment.

Aging is associated with changes in fractal scaling in the cardiovascular dynamics (Beckers et al., 2006; Goldberger et al., 1984; Goldberger et al., 2002a; Goldberger et al., 2002b; Goldberger, 1996; Goldberger, 1997; Iyengar et al., 1996; Lipsitz et al., 1990; Lipsitz and Goldberger, 1992; Lipsitz, 1995; Pikkujamsa et al., 1999). However, there is no information on memory length and controllability of cardiac rhythm in aging. Therefore, in the present study we assessed the effect of aging on memory length in inter-beat interval time-series.

# Materials and methods

Forty normal volunteers were selected from Fantasia database (Goldberger et al., 2000). These, as previously described (Peng et al., 2002), included 20 young (mean age 27, range 21–34 year) and 20 elderlies (mean age 74, range 68–81 year) subjects. Each group consisted of 10 women and 10 men. All participants signed informed written consent and underwent a screening medical evaluation and electrocardiogram (ECG) to assure that they were in good health.

Subjects laid supine for 120 min while continuous ECG signals were collected. All subjects remained in a resting, inactive state while watching the movie ‘‘Fantasia©’’ in order to maintain wakefulness. The continuous ECG signals were digitized and sampled at 250 Hz. The R peaks were detected and the R-R interval series were generated using Chart software (version 5, ADInstrument). The R-R interval series was visually inspected and artifact-free continuous R-R intervals were selected for inverse statistical analysis as described (Mazloom et al., 2014).

Details of this analysis are described elsewhere (Ebadi et al., 2011; Shirazi et al., 2013). Briefly, in this method we find the event- "rare" event- that is ρ seconds slower (or faster) than a specific point in the time-series. The time (τ) needed to observe a rare event in the time-series is defined as the "exit time". The inverse statistic (which allows comparison of data sets with different variability) calculates distribution of the exit times in a given time-series (Ebadi et al., 2011). Then, we compared this distribution with its shuffled version as described (Ebadi et al., 2011; Shirazi et al., 2013). Original and shuffled data are only different within small τ regions, and after they cross there is no difference. "Memory length" of time-series quantifies the previous data that affect the present data point (Shirazi et al., 2013). Furthermore, $\Delta\beta \geq \rho$ shows the distribution of decelerating rare events and if $\Delta\beta \leq -\rho$ we can look at the distribution of accelerating rare events (Shirazi et al., 2013).

**Statistical analysis**

All time-series were normalized to have SD = 1. Data were presented as the mean±SEM and were analyzed using GraphPad Prism 5. Statistical comparison between young and elderly groups was performed using two-way ANOVA and Bonferroni’s post-hoc test. A *P* value of <0.05 was considered statistically significant.

# Results

Inverse statistics was used to investigate the dynamics of R-R interval series. Figure 1 shows the exit times distribution for the levels of $\rho = 0.5\sigma$ (σ is the standard deviation of the R-R interval time-series) in healthy young and elderly subjects, and the corresponding shuffled data when $\Delta\beta \leq -\rho$. As shown in this figure, although the distribution of the time-series crosses the shuffled distribution in both groups, the probability curve soon overlaps with the shuffled data curve in the young subjects. Moreover, the exit time distribution curve has a tendency to overlap with the shuffled curve in this group (Fig. 1a). In contrast, in elderly subjects there is a significant difference between the original and shuffled sets ($P<0.05$) (Fig. 1b).

The ‘memory length’ ($\tau_m$) values for observing a decelerating ($\Delta\beta \geq \rho$) and accelerating ($\Delta\beta \leq -\rho$) rare event at different ρ levels (from $0.25\sigma$ to $3\sigma$) were also calculated (Fig. 2). There is a significant

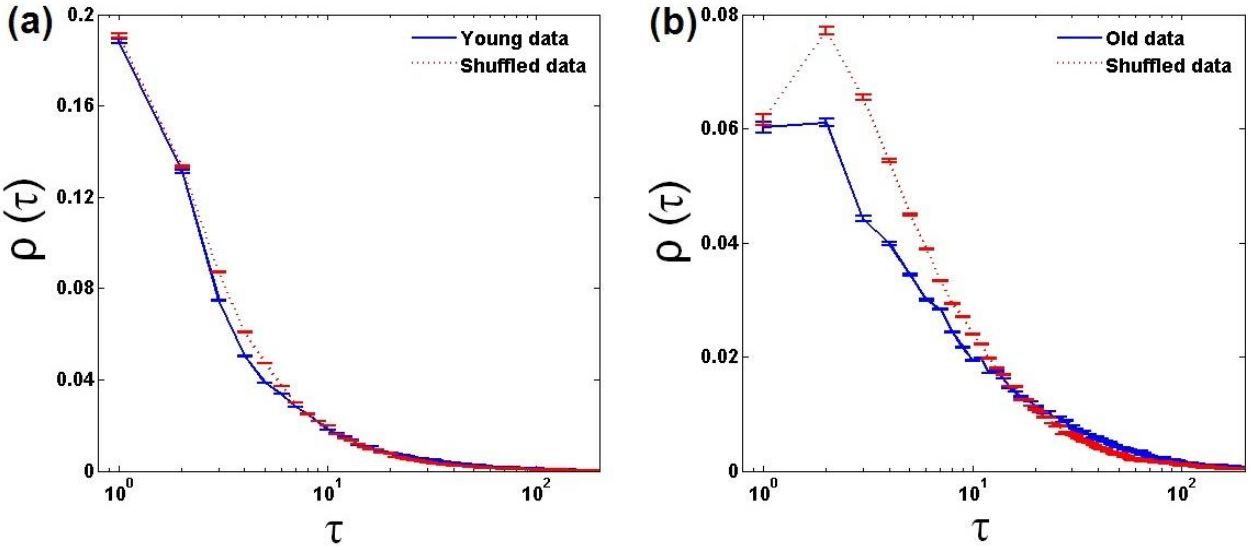


**Fig.1.** The probability distribution of exit times (τ) needed to observe an accelerating event that is ρ = 0.5σ second faster than a given point (t) within the R-R interval time-series. Blue solid lines represent probability distribution of τ of the original time-series and red dot lines correspond to their shuffled time-series. Data are presented as mean±SEM.

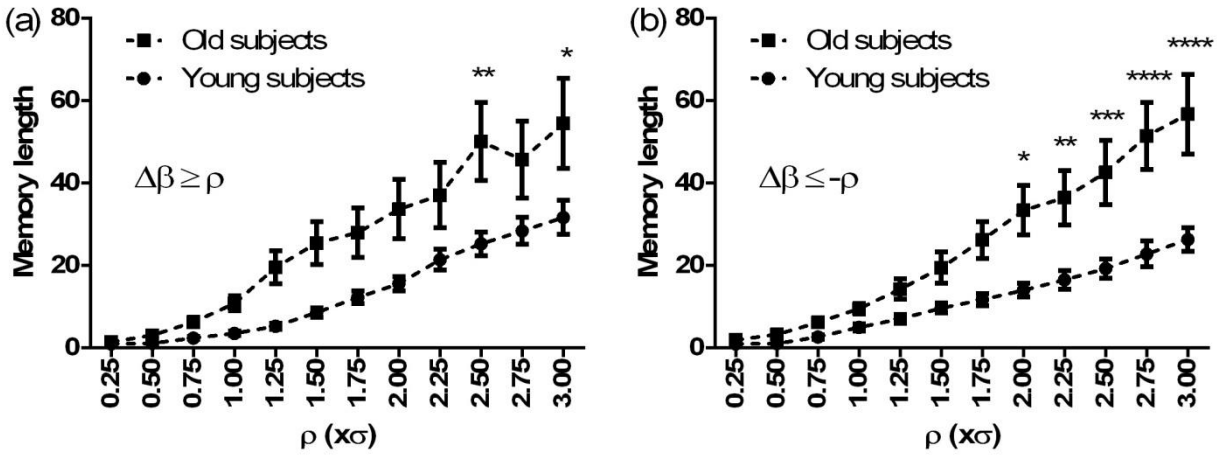


**Fig.2.** Comparison of memory length ($\tau_m$) of the cardiac inter-beat interval time-series for observing a decelerating (a) and accelerating (b) event with varying thresholds (from 0.25σ to 3σ) between the young and elderly groups. Data are shown as the mean±SEM. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, $^{****}P<0.0001$ in comparison with the young group.

difference in $\tau_m$ between two groups in terms of observing both decelerating ($F_{group}$ = 18.29, $P<0.0001$) and accelerating ($F_{group}$ = 22.84, $P<0.0001$) rare events. Two-way ANOVA also shows that regardless of the groups, $\tau_m$ increases when ρ is set for both decelerating and accelerating rarer events ($F_\rho$ = 44.35, $P<0.0001$ and $F_\rho$ = 68.03, $P<0.0001$; respectively).

As shown in Figure 2a, $\tau_m$ was significantly higher in elderly subjects only when the decelerating rare events were defined as ρ = 2.5σ ($P<0.01$) and ρ = 3σ ($P<0.05$). Regarding accelerating rare events, the memory length of young and elderly hearts are significantly different at each level when ρ is larger than 2σ (Fig. 2b).

## Discussion

In the present study, we used an inverse statistical approach and calculated the memory length to provide new information about age-related alterations in controllability of cardiac rhythm. Our results showed that time distribution curve in young subjects is closer to shuffled curve, and there is a longer

memory length in elderly subjects for both decelerating and accelerating rare events in cardiac time series.

Complexity of cardiac dynamics degrades with aging in studies using different analytic techniques (Beckers et al., 2006; Goldberger et al., 1984; Goldberger et al., 2002a; Goldberger et al., 2002b; Goldberger, 1996; Goldberger, 1997; Iyengar et al., 1996; Lipsitz et al., 1990, Lipsitz and Goldberger, 1992; Lipsitz, 1995; Pikkujamsa et al., 1999) were reported. Iyengar et al. (1996) suggest there may be a breakdown in the fractal-like behavior of inter-beat interval fluctuations with healthy aging. Also Kaplan et al. (1991) showed lower approximate dimension and approximate entropy in the heart rhythm of old group than the young. This loss of complexity appears to be due to the age-related impairment in the function of different systems. For instance, the physiologic aging process leads to dropout of sinus node cells (Wei and Gersh, 1987), ß-adrenoceptor response change (Wei and Gersh, 1987), reduction in parasympathetic tones (Lipsitz et al., 1990) and alteration in circadian hormonal and temperature rhythms (Lipsitz, 1996).

We have recently suggested inverse statistics to analyze time-series in physiological rhythms. Using this method, we found that the original heartbeat time-series is more similar to the shuffled time-series in young compared to elderly subjects. This means that at any given exit time, it is less likely to observe a defined accelerating event in comparison with the shuffled data set in elderly subjects. More intuitively, it is more likely that an accelerating event (e.g. tachycardia) is followed by further, similar events in elderly compared to young subjects.

We also calculated "memory length" in cardiac time-series using inverse statistics. Although the concept of memory has its own definition in different contexts, it is widely used in the life sciences, but not specifically in cardiac physiology. In the analysis of time-series, memory is a statistical characteristic that differentiates the time-series from random, memory-less processes. The novel feature of our method is its changeable, pre-defined level for observing a "rare" event, which carries the information of the system's behavior and make it level-dependent (Shirazi et al., 2013). This approach gives empiric evidence that the memory of "rare" fluctuations in cardiac cycles is prolonged in pathologic conditions such as heart failure, cirrhotic cardiomyopathy and endotoxaemia, comparing with healthy condition (Mazloom et al., 2014; Shirazi et al., 2013). A longer memory length is defined as the longer time that a physiological rhythm can be affected by a sudden decelerating event. Our results showed that heartbeat rhythm has a short memory around its average region, but a longer memory length following more scarce fluctuation; a phenomenon which is more prominent in elderly subjects. Also, we found a longer memory length in the elders' heartbeat time-series compared to young hearts in respect to observing both accelerating and decelerating rare events. This may indicate that a sudden decelerating event could potentially affect the cardiac rhythm of elderly subjects for a longer duration than young subjects. Thus, if an accelerating or a decelerating cardiac event occurs in a young person, it will be 'forgotten' earlier than in an elderly.

Control systems are characterized by controllability, which is a useful concept in different fields (Liu et al., 2011; Raoufy et al., 2017). In the control theory a controllable system is described as a system that can be driven from its initial inputs to a desired state within a limited time (Liu et al., 2011). Although well-developed tools are available to calculate controllability in dynamical systems, they are not extensively used in physiological systems. Memory is estimation of the order of a time-series dynamical equation (Shirazi et al., 2013). Thus controllability is affected by the concept of memory in a time-series; intuitively control a system with prolonged memory is also harder. A high controllability is needed to respond rapidly to the environment; therefore, an increased memory length is potentially a disadvantage for an adaptive system such as cardiac autonomic regulation (Mazloom et al., 2014). Hence, the increased memory length in an aged cardiovascular system may indicate the decreased controllability of the system. The exact mechanism of increased memory length is not understood in pathological conditions. We have recently reported that systemic inflammation can increase the memory length of isolated perfused heart *in vitro* (Mazloom et al., 2014). This indicates that cardiac pacemaker dynamics can be affected by systemic inflammation and we should not expect to explain changes in heart rate dynamics only through alterations in autonomic nervous system (Gholami et al., 2012; Mazloom et al., 2014; Schmidt et al., 2007).

# Conclusion

In conclusion, we found that aging alters heart rate dynamics toward the prolongation of memory. Since the concept of memory has a direct implication in quantification of controllability, the increased memory length of the cardiac time-series in elderly subjects may indicate the reduced controllability of the system.

## Acknowledgments

We thank Amir Hosein Shirazi, PhD, for assistance with the analysis of memory length.

## Conflict of interest

The authors declare no conflict of interest.

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