Chaotic Signatures of Heart Rate Variability and Its Po
Aging and Heart Failure

Guo-Qiang Wu, Natalia M. Arzeno, Lin-Lin Shen, Da-Kan Tang, Da-An Zheng, Nai-Qing Zhao, Dwain L.

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Abstract

A paradox regarding the classic power spectral analysis of heart rate variability (HRV) is whether the charac
represent stochastic or chaotic phenomena. Resolution of this fundamental issue is key to unraveling the m
noninvasive marker for cardiac mortality risk assessment and stratification in congestive heart failure (CHF)
techniques of nonlinear time series analysis generally lack sufficient sensitivity, specificity and robustness to
the chaos level. Here, we apply a 'litmus test' for heartbeat chaos based on a novel noise titration assay wh
measure of the relative chaos level. Noise titration of running short-segment Holter tachograms from healthy
dependent) heartbeat chaos that was linked to the HF component (respiratory sinus arrhythmia). The relativ
subjects despite proportional age-related decreases in HF and LF power. In contrast, the near-regular heart
punctuated by undetected ectopic beats and other abnormal beats, causing transient chaos. Such profound
chaotic and spectral characteristics of HRV were accompanied by little changes in approximate entropy, a m
of HRV in these subject groups reveal distinct autonomic, cardiac, respiratory and circadian/sleep-wake me

Figures

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Introduction

Since its introduction in 1981 [1], power spectral analysis of heart rate variability (HRV) has become a stand
[4]. Numerous studies have demonstrated the prognostic power of the high- (HF) and low-frequency (LF) sp
predict mortality in cardiac patients, especially congestive heart failure (CHF) patients (reviewed in [6], [7]).
using linear Fourier theory and linear models such as transfer function [8], sympathovagal balance ([9], but
they clearly could also come from nonlinear processes.

In recent years there has been increasing recognition that HRV may in fact represent a much more comple
cardiac-autonomic outflows [13], [14], [15] in a fractal [16], [17] or entropic [17], [18], perhaps chaotic manne
/stochastic descriptions of HRV present a dilemma in interpreting its power spectrum. Definitive testing of th
physiologic mechanisms underlying HRV, which is critical to its proper use as a noninvasive marker for card
other cardiac diseases.

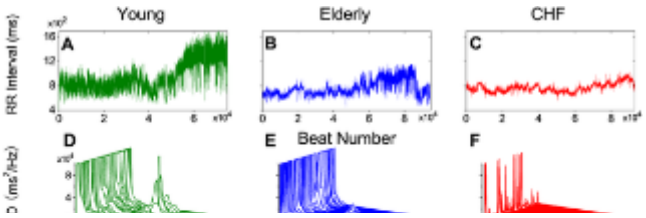
However, prevailing tests of chaotic dynamics using myriad nonlinear or complexity measures generally lac
discriminate chaos from random noise, much less quantify the chaos level (see Appendix S1 for critique of r
standpoint, it is not critical whether the detected chaos is completely deterministic or part stochastic so long
[22], [23] (see Appendix S1 for definitions of deterministic chaos and stochastic chaos). Moreover, the limite
systematic delineation of any time-dependent variations of the underlying nonlinear or chaotic dynamics of H
nonlinear HRV analysis have led to repeated failures to detect chaos in HRV [24], [25], [26] and lingering co
pathophysiological implications, or sheer stochastic with few mechanistic insights demonstrable beyond the

To resolve this fundamental dilemma once and for all, two critical research requirements must be met [23]. F
specificity and robustness in distinguishing chaos from random noise must be in place. Second, a rich data
dependent variations of the heartbeat chaos to be discerned and correlated with changes in pathophysiolog
based on a novel noise titration assay [28] which has proved to provide a robust, specific and time-resolved
time series [29], [30], [31]. We apply this powerful technique to the analysis of short-segment Holter tachogr
known time- and disease-dependent changes in HRV. Our results identified circadian-dependent heartbeat
sinus arrhythmia, RSA [32]) in young/elderly subjects, and transient heartbeat chaos which was linked to sp
the mechanisms of chaotic HRV and their physiologic and pathophysiologic determinants in health, aging ar

Results

Circadian rhythms of HRV in health, aging and CHF

Figure 1 illustrates the circadian heartbeat rhythms in three subject groups with decreasing HRV: young, eld
Both the young and elderly groups showed significant nocturnal increases of mean RR interval (Figs. 1A–1E
changes that mirrored the nocturnal increases of vagal-cardiac tone [33] which mediates the HF component
which restrains it [36], [38]. Nocturnal increases of LF power were much lower. The circadian variations of th
are consistent with those reported previously [39]. These spectral components and their circadian variations
CHF group (Figs. 1F; 1L). The lack of circadian rhythm in the HRV power spectrum of the CHF group was ir
interval (Figs. 1C; 1I) possibly reflecting corresponding changes in sympathetic outflow (which is generally a



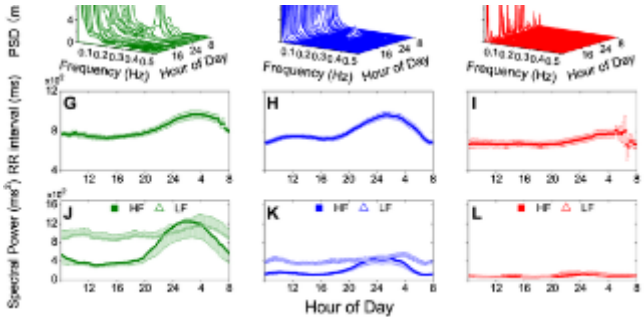


Figure 1. Circadian heart rate variability and mean beat-to-beat (RR) interval in young (green) or e heart failure (red) as revealed by Holter recordings (sampling rate was 128 Hz for the young grou elderly group).
A–C: 24-hr RR interval tachogram in one representative subject from each group. D–F: Corresponding s in Hz evaluated by standard autoregression methods [2] at 30-min intervals. G–I: Mean RR intervals (±S (0.15–0.4 Hz) and LF (0.04–0.15 Hz) power. Data points for G–L were evaluated at 12-min intervals and subject before group averaging.
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Mean and transient heartbeat chaos

To test whether such circadian-, age- and disease-dependent HRV power spectra signified random noise or and discriminated it from background physiologic noise (noise floor) by statistically comparing the goodness to successive short (12-min) time segments of the 24-hr RR interval series. Once nonlinearity was detected subjecting the data to a novel noise titration assay (see Methods). Because the latter relies on noise titratior robust to the attendant noise floor. Indeed, because of inevitable 'auto-titration' of experimental data by the l alone constitutes a sufficient proof of the presence of chaos [28]. This analytical approach therefore circumv contamination of experimental data that frustrate other methods of chaos detection (see Appendix S1).

We used two noise titration measures to assess the changes in chaos level. The detection rate (DR, which g of all time segments in which nonlinearity is detected within a 3-hr time window (see Methods). Figure 2A sh a young subject (particularly during nighttime) indicating a decrease of mean heartbeat chaos level in CHF,

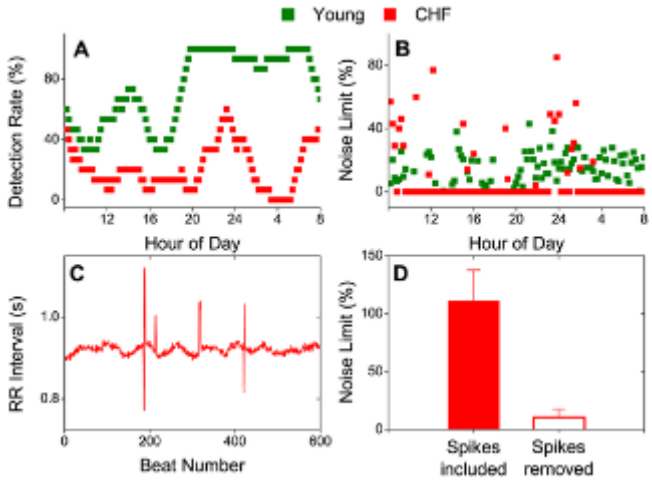

Figure 2. Noise titration assay of mean and transient heartbeat chaos.
A. Nonlinear detection rate in a young subject and a CHF patient, evaluated for a moving 3-hr time wind subjects evaluated for consecutive 12-min segments without moving-averaging. Time segments where r

zero noise limits. C. Example RR interval segment in the CHF patient showing sporadic spikes comprise beats such as post-ectopic compensatory pauses (see Methods). The high noise limit of 134.2% in this s after the spikes were manually removed. D. Statistical analysis of noise limits with and without (removed detected segments in 7 CHF subjects showing the highest noise limits.
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Next, we estimated the chaos level directly in each segment by using a highly time-resolved measure called shown [28] to correlate with the equivalent Lyapunov exponent (a gold-standard measure of chaos level [43 measures the relative chaos level (i.e., chaos level less the noise floor) and hence is more robust to noise c exponent (see Appendix S1).

Surprisingly, in those segments in which nonlinearity was detected, the measured NLs tended to be higher i noise titration data in this patient revealed irregular, infrequent, moment-to-moment alternations between ab all day long, indicating that HRV vacillated sporadically between chaos and non-chaos (or non-detection of segments showed that such transient heartbeat chaos was largely the result of RR interval spikes (Fig. 2C, careful and exhaustive searching efforts; see Methods) and other abnormal beats such as post-ectopic paus

Chaotic vs. spectral and entropic measures of HRV: circadian and CHF-deper

To compare these chaotic measures with traditional measures of HRV, we calculated the corresponding LF spectral power [2], [9]) and approximate entropy (ApEn, a measure of signal irregularity [44], [45]) in the thre were not significantly different in the young and elderly groups, and both exhibited similar diurnal/nocturnal normal heartbeat was circadian-dependent and not influenced by aging. These salient characteristics of DR again with no significant differences between the young and elderly groups (Fig. 3C).

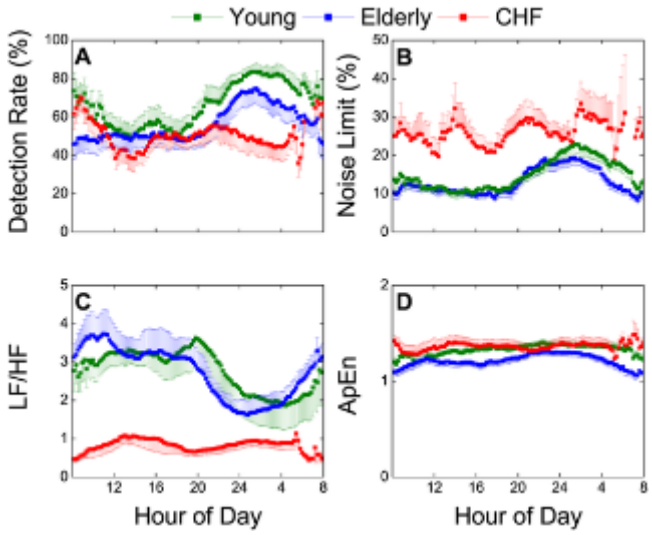

Figure 3. Chaotic vs. spectral and stochastic measures of heart rate variability in young, elderly a A. Detection rate (DR). B. Noise limit (NL). C. LF/HF power ratio. D. Approximate entropy (ApEn). The a significantly different between the young and elderly groups (repeated measures ANOVA, P>0.1) but we group had significantly different ApEn values than the young group (P = 0.02) and CHF group (P = 0.04) were marginal (P = 0.61).
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In comparison, the CHF group demonstrated significantly lower DRs yet higher NLs throughout much of the increased transient heartbeat chaos levels with little circadian variations (cf. Fig. 2). LF/HF was also signific

(Fig. 3C).

By contrast, ApEn did not vary significantly throughout the day in all groups and was marginally different bet profound circadian-, age- and CHF-dependent changes in HRV chaotic and spectral characteristics (Figs. 3. heartbeat chaos or a marker of its physiologic and pathophysiologic determinants.

HF chaos in health and aging vs. transient heartbeat chaos in CHF

Next, we examined the relations between these chaotic and spectral measures of HRV in the three subject g NL (Fig. 4B) in the young/elderly groups (and only weakly so in the CHF group). DR correlated strongly and CHF group (Fig. 4C), further demonstrating its significance as a measure of mean but not transient heartbea not at all) with HF and LF in the CHF group (Figs. 4D–4G), in agreement with the transient nature of the hea

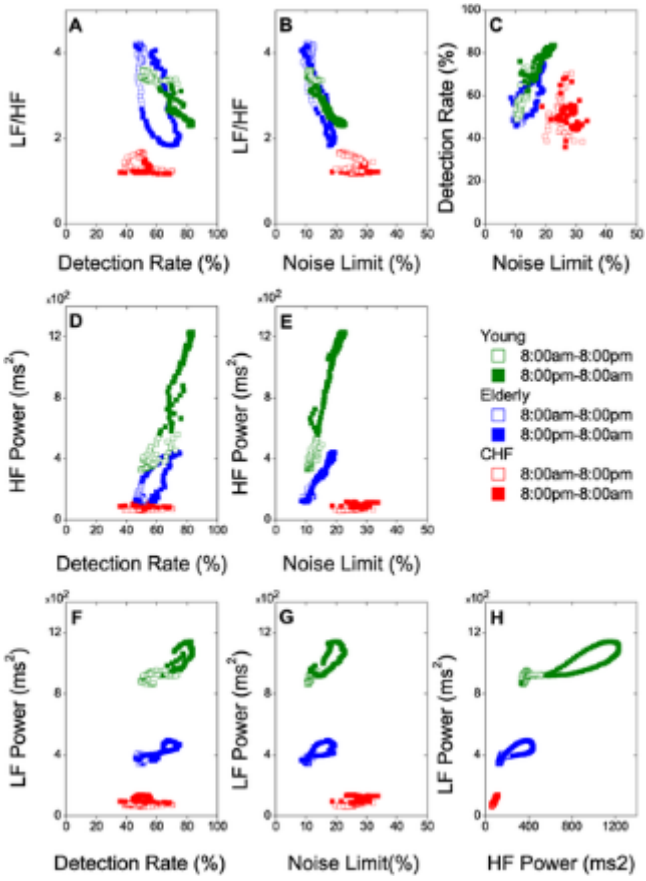

Figure 4. Correlations between chaotic and spectral indices of HRV.
Data are average values from each group. Open symbols, daytime; filled symbols, nighttime.
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By contrast, DR and NL correlated strongly and positively with HF power and only weakly with LF power in t their corresponding negative correlations with LF/HF (Figs. 4A–4B). These data when taken together show young and elderly subjects. Although the LF component might also contribute a minor fraction of the chaotic with DR and NL, such correlations could be secondary to its circadian parasympathetic-mediated covariatio to the chaotic dynamics of RSA in young/elderly subjects as 'HF chaos.'

Circadian chaotic and spectral discriminants of HRV in health, aging and CHF

All subject groups could be readily discriminated by the circadian variations of the chaotic and spectral char alone effectively distinguishes the young/elderly groups from the CHF group during specific times of the day 3A–3C; 4A–4C). All three groups could be distinguished from one another based on HF or LF power alone t effectively so when combined with DR or NL (Figs. 4D–4G), or when HF and LF were plotted together (Fig. was plotted against DR, NL or HF during either daytime or nighttime or both (Figs. 4F–H). Groups can be te multiple chaotic and spectral measures are plotted against one another in higher dimensions (not shown). N demonstrated here takes into account the temporal (circadian or transient) variations of the chaotic and spe sensitive than previous fractal-based discrimination approaches that relied on 24-hr HRV data [18], [46].

Discussion

The present study distinguishes itself from all previous studies of HRV by employing a litmus test for heartbe characteristic circadian- and disease-dependent changes in the HRV power spectrum that are closely relate traditional nonlinear or complexity methods that lack sufficient sensitivity, specificity and robustness in discri noise titration approach allowed us to not only discern heartbeat chaos but characterize it in a quantitative n making it possible for the first time to correlate the circadian- and disease-dependent changes in heartbeat spectrum. As discussed below, our results reveal distinct chaotic signatures of HRV which can be ascribed t that distinguish health and aging from CHF.

Chaotic signatures of HRV

Our noise titration results provide the strongest evidence yet that HRV in health and in CHF indeed demons sleep/wake)-dependent and the other transient. In both circumstances the HRV proves chaotic even though the chaos was completely “deterministic” or part “stochastic” (see Appendix S1). Such semantic issues asid chaotic signatures of HRV presently identified are not mere stochastic phenomena and must involve a stron closely with time-, aging- and disease-dependent changes in HRV and its power spectrum that were not trac physiologic and pathophysiological determinants of heartbeat chaos that distinguish health and aging from C

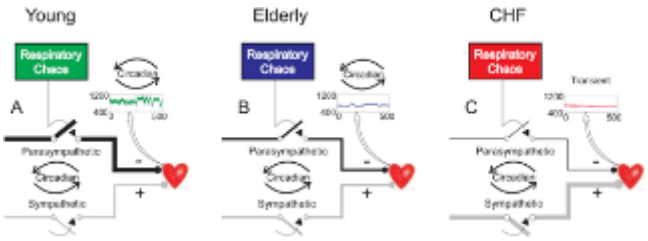

Figure 5. Mechanisms of high-frequency (HF) and transient heartbeat chaos in young, elderly and Insets show representative 500-beat segments of RR interval series. A. In young subjects, chaotic respi heartbeat via preganglionic temporal gating (denoted by switches) of vagosympathetic outflows [35] and arrhythmia. Respiration confers the chaotic dynamics of the HF component whereas vagal-cardiac tone power) relative to noise floor (LF power). Hence LF/HF is reciprocal to the S/N of HF chaos. Parasympat power, whereas sympathetic outflow does the opposite (+). Nocturnal increases of parasympathetic outfl corresponding circadian (curved arrows) variations of the S/N of HF chaos and hence, DR and NL. B. El parasympathetic-mediated HF and LF power, with almost invariant LF/HF compared with young subjects young subjects because the effective S/N are largely unchanged even though the intensity of HF chaos CHF patients, parasympathetic-mediated circadian HF and LF power are greatly suppressed and transie emerges.
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Mechanism of HF chaos in health and aging

LF/HF as inverse signal-to-noise ratio (S/N) of HF chaos.

Our results suggest that the chaos in the normal heartbeat is ascribable largely to RSA. This finding is consi component in healthy subjects remained chaotic (with a significant NL) even when all other components we short data segments (12 min duration), the very- or ultra-low-frequency components have only minimal effe physiologic noise floor that auto-titrates the HF chaos when evaluating short-segment DR and NL in healthy power spectrum, also provides a nonlinear measure that is roughly reciprocal to the S/N of HF chaos in this LF/HF with both DR and NL in the young/elderly groups (Figs. 3A–3C, 4A–4B). It should be noted, however in the LF component in other circumstances. Thus LF/HF is not a universal measure of S/N of HF chaos an case.

Respiratory and vagal-cardiac determinants of HF chaos level.

Such HF chaos in young/elderly subjects is ascribable at least in part to the recently reported chaotic dynam titration) [29], [31] — which may induce RSA via its gating of preganglionic vagal-cardiac neural activity [35] baroreflex [48]). A significant contribution of respiratory chaotic dynamics to heartbeat chaos is also support young subjects is strongly modulated by voluntary breathing, such as during speech or breath holding [48]. pacemakers responsible for generating the respiratory rhythm [49] are indeed capable of producing a chaoti dependence on initial conditions [30]. The available evidence and present results, when taken together, sug dynamics of RSA whereas cardiac-autonomic tones modulate the resultant chaos level (Fig. 5A). According 1J–1K) mediated by increases in vagal inhibition and decreases in sympathetic opposition [36], [38] result ir corresponding decreases in LF/HF; Fig. 3C) and hence, in DR and NL (Figs. 3A–3B). This model therefore circadian correlations of DR and NL with the HF component, and their negative circadian correlations with L

The circadian parasympathetic-sympathetic modulation of HF chaos may be intrinsic to the circadian clock in sleep stages, changes from supine to upright postures during the sleep-wake cycle, or changes in diurnal these factors to the diurnal-nocturnal changes in HF chaos should be addressed in future studies.

Age-invariance of relative HF chaos.

This model also explains why DR and NL were relatively unaffected by aging despite corresponding decrea decreases of HF and LF power with aging (Figs. 1J–1K) in the face of normal circadian variations of RR inte baroreflex sensitivity [40], [50], which may influence the LF component [51] as much as the HF component significant age-dependent decreases in HF chaos level (as measured by the HF power), the S/N of HF chao unchanged. Such aging-related parallel decreases of the HF and LF components keep the relative HF chao age-invariant.

Mechanism of transient heartbeat chaos in CHF

Absence of HF chaos in CHF.

The present results confirm that DR is decreased in CHF compared with healthy subjects, as reported previ nighttime when parasympathetic/sympathetic-dependent HF chaos in the young/elderly subjects climaxed. I in CHF reflects an absence of HF chaos, an effect which is unrelated to aging but represents a direct conse

Transient heartbeat chaos in CHF.

In addition, our noise titration results reveal pronounced transient heartbeat chaos precipitated by sporadic cardiac dynamics in CHF (Fig. 5C). Such transient chaos was evident even after our careful and exhaustive Methods). Presumably, such transient chaos would be even more pronounced and perhaps more complex (

been included in our assay.

Traditionally, HRV has been used primarily as a probe of autonomic regulation; any attendant ectopic beats their elimination often proves challenging especially in bulk [53]. In CHF, HRV is greatly suppressed and is r and hence is not readily amenable to quantitative analysis. Previous studies using Poincaré plots or other g increased complexity in some elderly subjects [54] and CHF patients [55], particularly those with marked sy such erratic HRV pattern was due to undetected ectopic beats and whether it represented increased HF cha The present results suggest that in CHF, transient chaos of HRV resulting from sporadic undetected ectopic compensatory pauses) *per se* may be of greater import than normal HF chaos (which is greatly attenuated i chaos may reveal valuable information about abnormal cardiac function that cannot be gleaned from examir alone (Fig. 5C). The contributions of varying types of ectopic beats and other abnormal beats (such as post- other erratic HRV patterns in CHF and their underlying pathophysiologic mechanisms deserve further study.

Conclusion

In conclusion, noise titration provides a robust, specific, time-resolved and quantitative assay for heartbeat c or entropic methods of HRV analysis. Our results based on this powerful analytical approach show that: (1) circadian- (or sleep-wake)-dependent chaos that is linked to RSA or the HF component. (2) The HF chaos l noise titration is modulated by changes in cardiac autonomic tones and is inversely proportional to LF/HF in chaos is absent but transient chaos emerges due to undetected ectopic beats and other abnormal beats su new measure of abnormal cardiac function in CHF. (4) The salient chaotic signatures of HRV in these subje circadian/sleep-wake mechanisms that distinguish health and aging from CHF. These findings provide a me chaotic and spectral characteristics of HRV as noninvasive markers for cardiac mortality risk assessment ar future.

Methods

Ethics statement

The study had been prior reviewed and approved by the MIT Committee on the Use of Humans as Experim reported anonymously.

Subjects

Recordings for the young group (n = 13, age 32±8 yrs mean±SD) and CHF group (n = 14, 56±12 yrs, all Ne conventional medical therapy but not β-adrenergic blockers) were from the PhysioNet database [57]. Recor suspected coronary artery disease but all with no history of myocardial infarction, CHF, respiratory dysfuncti Appendix S2 for further details and Appendix S3 for a listing of individual 24-hr RR interval data). Young sub elderly subjects and CHF patients but the ages of the latter groups were not significantly different (P>0.1, LS

Extraction of RR intervals

Subjects in all groups were selected on the basis of stability of the mean heart rate and limited number of ec were extracted from annotated Holter recordings by using an algorithm (Cygwin) provided by PhysioNet whi or missing beats and other ectopic beats [57]. To minimize recognition artifact [58], all remaining ectopic bea beats with abnormal QRS complexes undetected by preprocessing were manually removed. For CHF subje preprocessing eliminated most of the premature beats and the resultant RR intervals were highly regular wit beats) and other abnormal beats such as post-ectopic compensatory pauses.

Heart rate variability analyses

Spectral analysis.

The power spectral density of the RR interval series was computed (without resampling) by using a linear au recommended by the Task Force [2]. The frequency unit for each series was converted from cycles/beat to l (c/b)/(mean RRI). Spectral components were evaluated as the integral of power spectral density within the L

Chaotic analysis.

The method of noise titration [28] offers a highly sensitive litmus test (sufficient proof) for chaotic dynamics a contaminated data segments. In this method, nonlinear determinism in a time series was first identified [21], autoregressive model (Eq. 1) with varying memory order (κ) and nonlinear degree (d) to optimally predict the 2):

$$y_n^{nonlin} = a_0 + a_1 y_{n-1} + a_2 y_{n-2} + \cdots + a_\kappa y_{n-\kappa} + a$$
$$+ a_{\kappa+2} y_{n-1} y_{n-2} + \cdots + a_{M-1} y_{n-\kappa} + \varepsilon(\kappa,$$

$$C(r) = \log \varepsilon(r) + {}^{r}/_{N}$$

In the above, ε is the modeling error; M is the total number of polynomial terms in Eq. 1; r is the number of le computation of $C(r)$; N is the total number of data points in the series. The parameters a_m in Eq. 1 were recu series with linear dynamics — was rejected if the best nonlinear model provided a significantly better fit to th statistics at the 1% significance level.

Once nonlinear determinism was indicated, white noise of increasing standard deviations was added to the nonlinearity was 'neutralized'. The noise limit (NL) was calculated as the percent of signal power added as r an average NL value was obtained by repeating the titration procedure 5–10 times. Under this scheme, cha relative measure of chaos intensity. Conversely, if NL = 0, then it may be inferred that the series either is not the background noise (noise floor) in the data [28].

Complexity analysis.

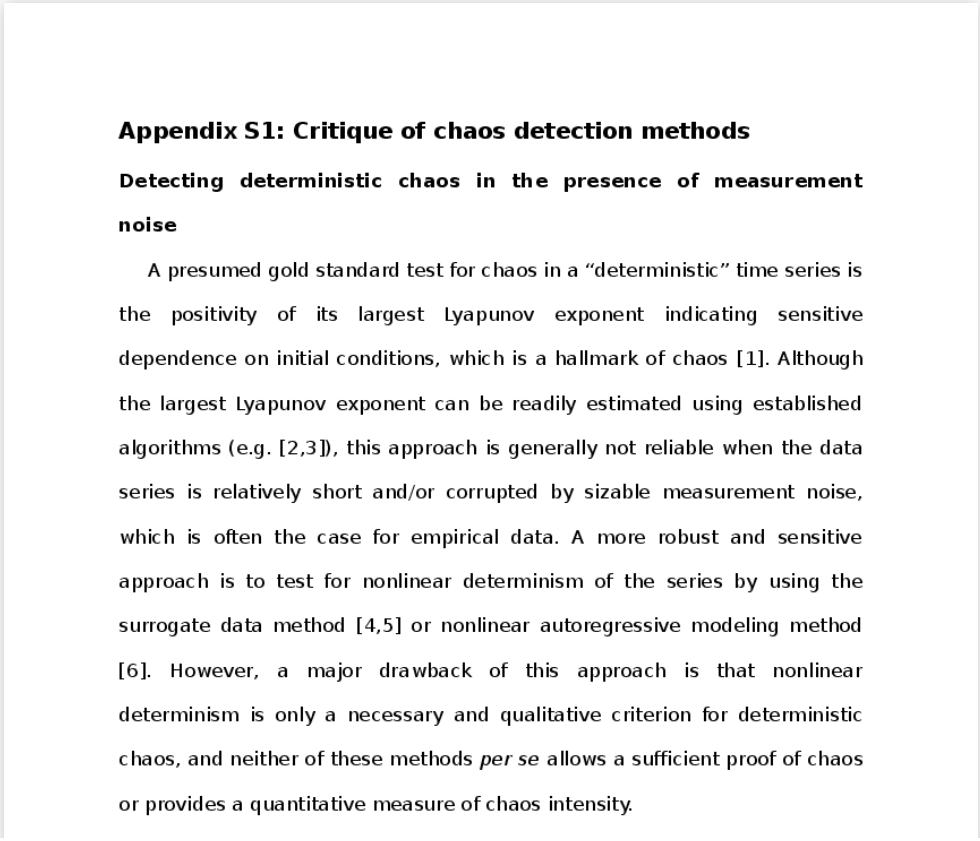
Approximate entropy (ApEn) was calculated as described elsewhere [45], [59] as a measure of the irregular index with an embedded dimension of 2 and a tolerance of δ (usually 0.1–0.25, here 0.2), which are typical

Data segmentation

To account for the nonstationarity of HRV, 24-hr heartbeat data were divided into 120 segments (12 min eac [21]. Nonlinear detection rate (DR) was calculated as the percentage of detected nonlinear segments in a 3- during the specific period. The window was centered on the present segment and moved one segment at a segment-by-segment and averaged over 15 segments in a similar fashion (the calculation of average NL ex were not included in the average).

Supporting Information

Appendix_S1.doc



Appendix S1: Critique of chaos detection methods

Detecting deterministic chaos in the presence of measurement noise

A presumed gold standard test for chaos in a "deterministic" time series is the positivity of its largest Lyapunov exponent indicating sensitive dependence on initial conditions, which is a hallmark of chaos [1]. Although the largest Lyapunov exponent can be readily estimated using established algorithms (e.g. [2,3]), this approach is generally not reliable when the data series is relatively short and/or corrupted by sizable measurement noise, which is often the case for empirical data. A more robust and sensitive approach is to test for nonlinear determinism of the series by using the surrogate data method [4,5] or nonlinear autoregressive modeling method [6]. However, a major drawback of this approach is that nonlinear determinism is only a necessary and qualitative criterion for deterministic chaos, and neither of these methods *per se* allows a sufficient proof of chaos or provides a quantitative measure of chaos intensity.

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Critique of chaos detection methods

Appendix S1.
Critique of chaos detection methods
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(0.12 MB DOC)

Appendix S2.
Description of the elderly group
doi:10.1371/journal.pone.0004323.s002
(0.05 MB DOC)

Appendix S3.
Individual elderly subjects data (Zip file)
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(2.51 MB ZIP)

Author Contributions

Conceived and designed the experiments: GQW CSP. Performed the experiments: GQW NMA. Analyzed th

reagents/materials/analysis tools: NQZ. Wrote the paper: CSP. Supervised the study: CSP. Contributed clini

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