Published in final edited form as:

J Biol Rhythms. 2008 June ; 23(3): 265–273. doi:10.1177/0748730408316166.

The Endogenous Circadian Pacemaker Imparts a Scale-Invariant Pattern of Heart Rate Fluctuations across Time Scales Spanning Minutes to 24 Hours

Kun Hu^{*,1}, Frank A. J. L. Scheer^{*,†}, Ruud M. Buijs^{†,‡}, and Steven A. Shea^{*,1}

^{*} Division of Sleep Medicine, Brigham and Women's Hospital, Boston, Massachusetts [†] Department of Hypothalamic Integration Mechanisms, Netherlands Institute for Brain Research, Amsterdam, The Netherlands [‡] Department Physiology, Instituto Biomedicas, Universidad Nacional Autónoma de México, Mexico City, Mexico

Abstract

Heartbeat fluctuations in mammals display a robust temporal structure characterized by scale-invariant/fractal patterns. These scale-invariant patterns likely confer physiological advantage because they change with cardiovascular disease and these changes are associated with reduced survival. Models of physical systems imply that to produce scale-invariant patterns, factors influencing the system at different time scales must be coupled via a network of feedback interactions. A similar cardiac control network is hypothesized to be responsible for the scale-invariant pattern in heartbeat dynamics, although the essential network components have not been determined. Here is shown that scale-invariant cardiac control occurs across time scales from minutes to ~24 h, and that lesioning the mammalian circadian pacemaker (suprachiasmatic nucleus; SCN) completely abolishes the scale-invariant pattern at time scales >~4 h. At time scales <~4 h, the scale invariance persisted following SCN lesion but with a different pattern. These results indicate previously unrecognized multiscale influences of the SCN on heart rate fluctuations that cannot be explained by a simple pacemaker of 24-h rhythmicity. The conclusion is that the SCN serves as a major node in the cardiac control network and imparts scale-invariant cardiac control across a wide range of time scales with strongest effects between ~4 and 24 h. These results demonstrate that experimental manipulations (e.g., SCN lesion) can be used to begin to model and understand the origin of scale-invariant behavior in a neurophysiological system.

Keywords

cardiac control; scale-invariant patterns; the suprachiasmatic nucleus (SCN); SCN lesion; network; feedback interactions

Scale-invariant patterns in heartbeat fluctuations: (1) persist during different behaviors and in varied environments, indicating that these patterns are intrinsic (Kobayashi and Musha 1982; Peng et al., 1995; Ivanov et al., 1999); (2) change with autonomic blockade and autonomic impairment indicating that they partly reflect autonomic regulation (Penttila et al., 2003; Beckers et al., 2006; Merati et al., 2006; Aoyagi et al., 2007); and (3) are affected by heart disease (Peng et al., 1995; Goldberger et al., 2002) and help to predict survival rates in patients

¹To whom all correspondence should be addressed: Kun Hu or Steven A. Shea, Division of Sleep Medicine, Brigham & Women's Hospital, Harvard Medical School, Boston, MA 02215; khu@bidmc.harvard.edu or Steven_shea@hms.harvard.edu.

after stroke (Makikallio et al., 2004) and in patients with acute myocardial infarction (Bigger et al., 1996), indicating that scale-invariant cardiac control may confer some health advantage. Existence of scale invariance in a given variable indicates that the fluctuations in that variable are similar at different time scales. This self-similarity across varied time scales is akin to the self-similar shape across different size scales observed in fractal patterns. Temporal scale invariance requires overall organization across different time scales, and can be generated by a network of feedback interactions among control nodes that operate at different time scales (Bak et al., 1987; Basu et al., 2004). In contrast, the lack of temporal scale invariance would indicate either influences on a variable from only one source with fluctuations only at one specific time scale, or simple additive influences from a number of control nodes that do not interact. Fluctuations in the variable influenced by such noninteracting systems will resemble random noise outside the single time scale being controlled. Scale invariance in heart rate fluctuations implies a network of coupled cardiac control nodes operating at different time scales to produce an overall scale-invariant pattern. However, no physiologically meaningful model yet has been established to account for such scale-invariant cardiac regulation.

The suprachiasmatic nucleus (SCN) in mammals generates self-sustained circadian oscillations that coordinate the near 24-h rhythms in many physiologic functions and behaviors (Schwartz, 2002). Disruption of the circadian rhythms is associated with increased cardiovascular morbidity and mortality (Knutsson et al., 1986; Kawachi et al., 1995; Penev et al., 1998; Davidson et al., 2006; Martino et al., 2007). One of the fundamental processes influenced by the SCN is heart rate, which displays clear ~24-h rhythms even under constant dark conditions, but loses circadian rhythmicity when the SCN is ablated (Saleh and Winget, 1977; Warren et al., 1994; Scheer et al., 2001). The circadian rhythm in heart rate is not simply caused by SCN-mediated circadian rhythms in locomotor activity, but is likely mediated by multisynaptic projections from the SCN to the heart, involving the sympathetic nervous system (Scheer et al., 2001). We recently discovered that the human circadian timing system also has strong influences on the temporal structure of heartbeat fluctuations that are independent of activity levels and lead to significant circadian rhythms in the scale-invariant pattern at time scales <1 h (Hu et al., 2004b). This finding also suggests that the SCN itself may impart a scale-invariant pattern in heart rate fluctuations but direct evidence is lacking, and data analysis and interpretation were limited to time scales <1 hour.

Mathematical models of physical systems reveal that scale-invariant patterns can be explained by interactions between multiple control system components that affect the overall system at different time scales (Bak et al., 1987; Basu et al., 2004). Similar complexity may be operating in numerous physiological systems via networks of coupled feedback loops (Ivanov et al., 1998; Ashkenazy et al., 2002). Assuming that mathematical models of physical systems are correct, then disruption of one of the major nodes of the network controlling heart rate—because of coupling within the network—ought to affect heart rate fluctuations at numerous time scales. We hypothesized that the SCN is a major node in this cardiac-control network rather than simply a generator of a periodic oscillation with a fixed ~24-h period, thus the SCN ought to influence cardiac control over a broad range of time scales. To specifically test this hypothesis, we examined the role of the SCN on scale-invariant patterns of heart rate. This was achieved by studying the heart rate signals of 7 rats with SCN lesion and 7 control rats without SCN lesion.

MATERIALS AND METHODS

The current study represents a reanalysis of heart rate data collected in a previously published study (Scheer et al., 2005). Locomotor data from the same study have been published elsewhere (Hu et al., 2007).

Data Acquisition

Heart rate recordings were made in Wistar rats (Harlan, Zeist, The Netherlands) throughout separate 10-day protocols in light/dark (12 h light:12 h dark; LD) and constant dark (0.1 lux; DD), as previously described (Scheer et al., 2005). Each rat lived individually in a cage with dimensions 39 × 38 × 38 cm. For the collection of heart rate data, a transmitter (CTA-F40; DataScience, St. Paul, MN) was implanted in each rat according to the Data Sciences International manual (DataScience). The rats were first anesthetized (0.8 mL/kg i.m. of Hypnorm and 0.4 mL/kg s.c. of Dormicum), and then the transmitter was secured to the inner muscle wall of the abdomen and the two electrodes were guided subcutaneously and secured to the muscles, one rostral and one caudal to the heart. After surgery, animals were allowed to recover for at least 2 weeks. Heart rate data were sent by the implanted transmitter in the freely moving rat to a telemetry antenna (RA1010; DataScience) that was positioned underneath the cage. Every 4 min, heart rate were sampled at 500 Hz for 10 sec and the average value in this interval was stored. In addition, core body temperature was also measured and sent by the transmitter every 4 min.

SCN Lesion

To ablate the SCN, 30 rats were first anesthetized with Hypnorm (0.8 mL/kg i.m.) and mounted in a stereotactic instrument (David Kopf Instruments, Tujunga, CA), as previously described (Scheer et al., 2005). Two electrode tips (0.2 mm diameter) were then placed bilaterally in the SCN (tooth bar at +5.0 mm; angle of -6° ; coordinates: -2 mm rostral to bregma, $+2$ mm to midline, 7.4 mm below brain surface) and heated at 80°C for 1 min (Scheer et al., 2005). To avoid the inclusion of rats with incomplete lesions, the day/night rhythms in drinking water were investigated at least 1 month after the surgery, and vasoactive intestinal polypeptide (VIP) and vasopressin (VP) within the SCN in perfusion-fixed brains (4% paraformaldehyde) were checked before data analyses, as described previously (Buijs et al., 1993; Kalsbeek et al., 1992). Rats with the presence of rhythms in drinking behavior, or with the presence of VIP or VP, were excluded from the study. Seven of the 30 rats met both behavioral and anatomical verification of complete SCN lesion. These SCN-lesioned rats (termed SCN_x) had heart rate recorded throughout the same 2 protocols (10 days in DD and 10 days in LD) as the control rats.

All experiments were conducted under approval of the Animal Care Committee of the Royal Netherlands Academy of Arts and Sciences and conformed to their guidelines on ethical use of animals. All efforts were made to minimize the number of animals used and their discomfort.

RESULTS

Mean Level and Circadian Rhythms of Heart Rate

In all control rats, heart rate displayed strong day/night rhythms (LD protocol) and circadian rhythms (DD protocol), as indicated by the peak at ~ 24 h in the power spectrum (Fig. 1A–D). As expected, the 24-h periodicity disappeared in SCN_x rats in both LD and DD (Fig. 1). However, the SCN lesion did not significantly alter the mean level of heart rate during either LD or DD when compared with control rats (mean heart rate: control LD = 342 ± 13 beats/min; control DD = 340 ± 11 ; SCN_x LD = 351 ± 16 ; SCN_x DD = 347 ± 18 ; $p > 0.2$; analysis of variance [ANOVA]).

Scale Invariance in Heart Rate Fluctuations

To quantify the scale-invariant patterns in the heart rate fluctuations, we performed detrended fluctuation analysis (DFA; Peng et al., 1995). The DFA method is a widely used technique for determining the existence of time scale-invariant patterns. It enables reliable estimates of scale-

invariant correlations in nonstationary signals—when statistical properties including mean and standard deviation are not constant over time (Hu et al., 2001; Chen et al., 2002). Using DFA, previous studies showed that the heartbeat fluctuations of rats possess scale-invariant positive correlations at time scales from 11 beats to ~2000 beats (corresponding to ~2 sec to ~6 min) (Beckers et al., 2006). Here we used DFA to quantify the detrended fluctuations $F(n)$ of heart rate in a different range of time scales n from ~12 min to 24 h. We analyzed all heart rate data collected during 10-day LD and 10-day DD protocols (3600 points for each rat). The results presented in Figure 2a show that rats with intact SCN possess a scale-invariant pattern of heart rate over the whole range of tested time scales. This scale-invariant pattern is demonstrated as a group mean scaling exponent (α) of 0.86 (individuals' α range = 0.73–0.96) on the log-log plot in Figure 2a. This α exponent of 0.86 indicates positive correlations—where large heart rate values are more likely to be followed by large values, and vice versa for small heart rate values (note: $\alpha = 0.5$ would indicate no correlation [white noise]). Moreover, there was no difference in rats when they lived under LD and DD conditions (Fig. 2). Specifically, $\alpha = 0.87 \pm 0.08$ during LD and 0.86 ± 0.04 during DD ($p > 0.5$, ANOVA).

Note that the scaling exponent obtained in this study is smaller than that previously reported in rat and in human ($\alpha \approx 1$). The difference is due to the fact that previous studies analyzed individual heartbeat intervals (time units) whereas in this study we used heart rate (frequency units) with signals sampled every 4 min based on 10-sec sampling. To demonstrate the effect, we performed the following simulation using 10-day beat-to-beat intervals collected from 5 healthy human subjects during both wakefulness and scheduled sleep opportunities while subjects lived in an individual laboratory suite. Beat-to-beat intervals were divided into nonoverlapping windows with the same size of 4 min. In each 4-min window, average heart rate was obtained based on the first 10 sec. We applied DFA to the original heartbeat intervals and to the resampled heart rate signals. The scaling exponent of the resampled human heart rate data ($\alpha = 0.84 \pm 0.07$) was similar to the exponent obtained in heart rate of control rats ($\alpha = 0.87 \pm 0.08$ during LD and 0.86 ± 0.05 during DD), but was smaller than that of original human heartbeat intervals (0.99 ± 0.04).

Effect of SCN Lesion on Cardiac Scale Invariance

Next we determined whether or not SCN lesioning influences the DFA scaling exponent (α), thus testing the hypothesis that the SCN operates as one of the major nodes of the control network regulating scale-invariant fluctuations in heart rate, thereby influencing heart rate over a very broad range of time scales (due to coupling between control nodes operating at different time scales). We found that SCN lesioning completely abolished the scale-invariant pattern, as indicated by DFA results, at time scales longer than 3.6 h (here termed α_2 time range) during both LD and DD, and that the SCN had a very different effect at time scales shorter than 3.6 h (Fig. 2). In the α_2 time range, the consistent values of the scaling exponents α_2 were close to 0.5 for all SCNx rats (mean $\alpha_2 = 0.46 \pm 0.11$ during LD and $\alpha_2 = 0.43 \pm 0.14$ during DD), indicating that correlations completely break down, and that heart rate fluctuations of SCNx rats resemble uncorrelated white noise at time scales larger than 3.6 h. In contrast, correlations of heart rate fluctuation over the time range from minutes up to 3.6 h (here termed α_1 time range) are changed but somewhat preserved following SCN lesion, with a significantly larger α_1 in SCNx compared with control rats (Fig 2; for SCNx, mean $\alpha_1 = 1.08 \pm 0.14$ during LD and $\alpha_1 = 1.05 \pm 0.12$ during DD; for control rats, mean $\alpha = 0.87 \pm 0.08$ during LD and 0.86 ± 0.04 during DD; $p < 0.004$, ANOVA). As with control rats, the light/dark cycle did not affect the correlation exponent in SCNx rats ($p > 0.5$, ANOVA).

Effect of Mean Activity Levels on Cardiac Scale Invariance

To test for independent influences of the mean level of activity on cardiac scale invariance, we compared cardiac scale invariance during the DD and LD while mean activity level changed.

Using the animals' inactive periods in both LD and DD protocols, we found no significant difference in cardiac scale invariance between LD and DD ($p = 0.13$; Fig. 3A) despite a 30% drop in mean activity levels during LD ($p < 0.0001$; Fig. 3B). For the active period, the scale invariance in heart rate was also similar in both DD and LD protocols ($p = 0.12$) whereas mean activity was significantly higher in LD than in DD ($p = 0.0006$; results not shown). Thus, cardiac scale invariance is not simply a result of absolute activity levels, but appears to be independently regulated.

Relationship between Scale Invariance in Heart Rate Fluctuations and Activity Fluctuations

To test whether dynamic interactions between fluctuations in heart rate and activity (independent of mean heart rate and activity) might contribute to scale invariant cardiac control, we determined the correlation between cardiac scale invariance and scale invariance in activity fluctuations. We found that cardiac scale invariance characterized by the scaling exponent was not related to the scale invariance of activity fluctuations in either DD or LD. This lack of significant correlation occurred during both the active and the inactive periods (Fig. 4).

DISCUSSION

In this study, we discovered that heart rate fluctuations possess robust scale-invariant patterns from minutes up to 24 h, and that lesioning the SCN leads to a breakdown of the scale-invariant patterns over a specific range of time scales (from ~3.6 to 24 h), with very different effects at $< \sim 3.6$ h. These findings provide clear evidence that the SCN is one of the key intrinsic factors contributing to scale-invariant patterns in heart rate fluctuations. Moreover, because the SCN has such a major influence over a very broad range of time scales (i.e., not only at a time scale close to 24 h), the SCN must be one of the principal nodes of the network controlling heart rate fluctuations.

The preservation of a scale-invariant pattern in heart rate fluctuations in SCNx rats at time scales < 3.6 h indicates that another neurophysiological source other than the SCN must be responsible for much of the scale-invariant patterns of heart rate over this shorter time range. The observation of similar correlations across the time scale from minutes to 3.6 h and across the time scale from 3.6 to 24 h in intact animals also implies that the SCN and the non-SCN mechanisms of cardiac regulation are coupled. Thus, our results strongly support the hypothesis of the existence of coupled intrinsic cardiac control nodes operating at different time scales (Fig. 5). The precise anatomical sites of the other components of such a multiscale regulator are unknown, and the nature of the interactions between the SCN and these components remains to be elucidated. It is also possible that the SCN itself contains interacting nodes that together are responsible for the scale invariance of heart rate fluctuations in the range of time scales from 3.6 to 24 h.

Establishing a physiologically meaningful model and understanding the origin of scale-invariant behavior in cardiac dynamics poses stimulating challenges for physiology, physics, and mathematics. The first crucial step is to map the anatomical architecture of a neurophysiological network responsible for scale invariance. Prior to this study no key elements of the cardiac control network contributing to scale-invariant behavior have been identified. We report a neural site (SCN) that is entirely responsible for scale-invariant cardiac regulation over a range of specific time scales ($> \sim 4$ h). This finding is surprising because the SCN, serving as the endogenous circadian pacemaker, has been thought to function mainly at a specific time scale, that is, generating and coordinating rhythms close to 24 h in many physiological systems. It is still unclear how the same neural site can generate a relatively stable rhythm at a fixed time scale (~ 24 h) and simultaneously display scale-invariant fluctuations over a wide range of time scales (~ 3.6 –24 h). Generally, such coexistence of rhythms and scale-invariant patterns in a system indicates nonlinear feedback coupling among rhythms and

fluctuations at different time scales. However, specific mathematical models are needed to explain the complex functions of the SCN at multiple time scales.

Separate Networks Responsible for Cardiac and Activity Scale Invariance

In our previous studies, we found similar scale-invariant patterns of activity fluctuations in rats and humans, and that such patterns were independent of mean activity levels and environmental influences (Hu et al., 2004a, 2007). Those findings indicated that, similar to heart rate fluctuations, there exists a complex control network influencing locomotor activity. It seems possible that the same network is responsible for scale invariance in the two physiological outputs such that the observed cardiac scale invariance is secondary to feedback control of locomotion. On the other hand, although mean activity can obviously influence mean heart rate, it is not necessarily the case that the fluctuations around the mean levels in two physiological signals are related—and it is the fluctuations that are being assessed in the “detrended” fluctuation analysis (because changes in the mean levels are subtracted). The ideal way to test whether cardiac scale invariance is independent of locomotion feedback is to control activity. This cannot easily be done in rats, as immobilization could lead to stress-related effects on heart rate. But it is relatively easy to achieve in humans. Indeed, we recently discovered a circadian rhythm of cardiac scale invariance in humans and that this rhythm persists throughout 38 h of voluntary inactivity (Ivanov et al., 2007). These findings indicate that activity and cardiac scale invariance in humans can be uncoupled. Moreover, we showed in this study that, as with humans, in rats (1) the cardiac scale invariance is essentially unchanged by changes in mean activity level (Fig. 3), and (2) activity scale invariance does not predict scale invariance in cardiac dynamics (Fig. 4). Therefore, we conclude that there are likely to be separate feedback networks responsible for cardiac and activity scale invariance.

Our results clearly indicate that the SCN is a major node in both control networks of heart rate and activity fluctuations. However, by ablating the entire SCN and looking only at the downstream variables, we cannot yet distinguish different effects from intervening parts of the control pathways. For example, the SCN could influence heart rate in a unique way (e.g., the locomotory and cardiac influences from the SCN may emerge from distinctly different parts of the SCN and have different patterns), or the SCN could influence many variables in the same scale-invariant manner. Even if the latter occurs, the feedback interactions for the different variables are likely to result in unique downstream patterns. Indeed, there are numerous possible sites where SCN’s influences and integration of information and pattern can occur, as there are multisynaptic pathways for control of both locomotion and heart rate (Scheer et al., 2001). Because autonomic impairment or blockade significantly alters cardiac scale invariance (Penttilä et al., 2003; Beckers et al., 2006; Merati et al., 2006; Aoyagi et al., 2007), the SCN-related autonomic regulation may potentially provide an explanation of the SCN’s contribution to cardiac scale invariance.

At the current stage, we still cannot identify neuronal pathways that are responsible for the SCN influence on cardiac and activity scale invariance. Nevertheless, our studies indicate clearly that (1) scale invariance is a universal characteristic of physiological fluctuations, and (2) the SCN is a major node in both scale-invariant control networks of activity and cardiac dynamics, imparting both activity and heart rate fluctuations over a wide range of time scales, especially at large time scales (>4 h). To confirm that the SCN is a major node in the network responsible for scale-invariant control of physiology, future studies could test whether a similar scale invariant pattern exists in temperature regulation.

Impact of Scale Invariant Cardiac Control on Physiology

The finding of scale-invariant heart rate fluctuations challenges the classical principle of homeostasis, which postulates that physiological systems return to equilibrium after

perturbation and that linear causality controls the pathways of physiological interaction. The cardiac scale invariance has been linked to situations found in physical dynamic systems far away from equilibrium. Such systems are comprised of a network of nonlinear feedback interactions and never settle down to constant output, but rather exhibit complex fluctuations (Stanley, 1971; Kurths et al., 1995; Shlesinger and West, 1998). Models of these physical systems imply that cardiac scale invariance may derive from a network of controlling factors operating at different time scales with feedback interactions, which lead to an overall organization of fluctuations (or rhythms) in heart rate signals at all time scales. For instance, factors that influence heart rate at varied time scales can include temperature changes, activity related influences, endocrine and autonomic influences, and influences internal to the heart itself. Alteration in cardiac scale invariance is associated with cardiovascular disease and predicts reduced survival (Bigger et al., 1996; Perkiomaki et al., 2001; Makikallio et al., 2004). Thus, analogous to some known physical systems, loss of the scale invariance of cardiac control may indicate a simpler physiological control system that is less adaptive to perturbations and is more vulnerable to disturbing events.

In this study we showed that the SCN is a major node in the network of cardiac control, and that the SCN lesion imparts temporal organization of heart rate fluctuations over a wide range of time scales. However, as noted above, our experiment was not designed to determine whether the SCN influence on cardiac scale invariance derives from neuronal interactions within the SCN, or the influence is generated by feedback interactions between the SCN and other neural sites influencing heart rate. Regardless of the underlying mechanisms, our results reveal previously unrecognized SCN contribution to scale-invariant behavior in cardiac dynamics, which can perhaps be used for the assessment of SCN-related pathological alterations. To fully understand scale-invariant cardiac control and to ultimately build a physiological network model, future studies could be directed at determining the anatomical sites of other components of such a multiscale cardiac regulator, and elucidating the nature of the interactions between the SCN and these components.

Acknowledgments

The research is supported by grants from NIH/NHLBI K24 HL076446 and R01 HL076409 to S.A.S. and a Pickwick fellowship to F.A.J.L.S.

References

- Aoyagi N, Struzik ZR, Kiyono K, Yamamoto Y. Autonomic imbalance induced breakdown of long-range dependence in healthy heart rate. *Methods Inf Med* 2007;46:174–178. [PubMed: 17347751]
- Ashkenazy Y, Hausdorff JM, Ivanov PCh, Stanley HE. A stochastic model of human gait dynamics. *Physica A: Statistical Mechanics and Its Applications* 2002;316:662–670.
- Bak P, Tang C, Wiesenfeld K. Self-organized criticality: An explanation of the 1/f noise. *Phys Rev Lett* 1987;59:381–384. [PubMed: 10035754]
- Basu S, Foufoula-Georgiou E, Porte-Agel F. Synthetic turbulence, fractal interpolation, and large-eddy simulation. *Phys Rev E* 2004;70:026310.
- Beckers F, Verheyden B, Ramaekers D, Swynghedauw B, Aubert AE. Effects of autonomic blockade on non-linear cardiovascular variability indices in rats. *Clin Exp Pharmacol Physiol* 2006;33:431–439. [PubMed: 16700875]
- Bigger JT Jr, Steinman RC, Rolnitzky LM, Fleiss JL, Albrecht P, Cohen RJ. Power law behavior of RR-interval variability in healthy middle-aged persons, patients with recent acute myocardial infarction, and patients with heart transplants. *Circulation* 1996;93:2142–2151. [PubMed: 8925583]
- Buijs RM, Kalsbeek A, Van der Woude TP, Van Heerikhuijsen JJ, Shinn S. Suprachiasmatic nucleus lesion increases corticosterone secretion. *Am J Physiol* 1993;264:R1186–R1192. [PubMed: 8322972]
- Chen Z, Ivanov PC, Hu K, Stanley HE. Effect of nonstationarities on detrended fluctuation analysis. *Phys Rev E* 2002;65:041107.

- Davidson AJ, Sellix MT, Daniel J, Yamazaki S, Menaker M, Block GD. Chronic jet-lag increases mortality in aged mice. *Curr Biol* 2006;16:R914–R916. [PubMed: 17084685]
- Goldberger AL, Amaral L, Hausdorff JM, Ivanov PCh. Fractal dynamics in physiology: Alterations with disease and aging. *Proc Natl Acad Sci U S A* 2002;99:2466–2472. [PubMed: 11875196]
- Hu K, Ivanov PC, Chen Z, Carpena P, Stanley HE. Effect of trends on detrended fluctuation analysis. *Phys Rev E* 2001;64:011114.
- Hu K, Ivanov PC, Chen Z, Hilton MF, Stanley HE, Shea SA. Non-random fluctuations and multi-scale dynamics regulation of human activity. *Physica A* 2004a;337:307–318. [PubMed: 15759365]
- Hu K, Ivanov PC, Hilton MF, Chen Z, Ayers RT, Stanley HE, Shea SA. Endogenous circadian rhythm in an index of cardiac vulnerability independent of changes in behavior. *Proc Natl Acad Sci U S A* 2004b;101:18223–18227. [PubMed: 15611476]
- Hu K, Scheer FA, Buijs RM, Shea SA. The circadian pacemaker generates an endogenous circadian rhythm in the heart fractal structure in rats. *Cardiovasc Res.* (in press).
- Hu K, Scheer FA, Ivanov PC, Buijs RM, Shea SA. The suprachiasmatic nucleus functions beyond circadian rhythm generation. *Neuroscience* 2007;149:508–517. [PubMed: 17920204]
- Ivanov PC, Bunde A, Amaral LA, Havlin S, Fritsch-Yelle J, Baevsky RM, Stanley HE, Goldberger AL. Sleep-wake differences in scaling behavior of the human heartbeat: Analysis of terrestrial and long-term space flight data. *Europhys Lett* 1999;48:594–600. [PubMed: 11542917]
- Ivanov PC, Hu K, Hilton MF, Shea SA, Stanley HE. Endogenous circadian rhythm in human motor activity uncoupled from circadian influences on cardiac dynamics. *Proc Natl Acad Sci U S A* 2007;104:20702–20707. [PubMed: 18093917]
- Ivanov PC, Nunes Amaral LA, Goldberger AL, Stanley HE. Stochastic feedback and the regulation of biological rhythms. *Europhys Lett* 1998;43:363–368. [PubMed: 11542723]
- Kalsbeek A, Buijs RM, Van Heerikhuize JJ, Arts M, Van der Woude TP. Vasopressin-containing neurons of the suprachiasmatic nuclei inhibit corticosterone release. *Brain Res* 1992;580:62–67. [PubMed: 1504818]
- Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Speizer FE, Hennekens CH. Prospective study of shift work and risk of coronary heart disease in women. *Circulation* 1995;92:3178–3182. [PubMed: 7586301]
- Knutsson A, Akerstedt T, Jonsson BG, Orth-Gomer K. Increased risk of ischaemic heart disease in shift workers. *Lancet* 1986;2:89–92. [PubMed: 2873389]
- Kobayashi M, Musha T. 1/f fluctuations of heartbeat period. *IEEE Trans Biomed Eng* 1982;29:456–457. [PubMed: 7106796]
- Kurths J, Voss A, Saparin P, Witt A, Kleiner HJ, Wessel N. Quantitative analysis of heart rate variability. *Chaos* 1995;5:88–94. [PubMed: 12780160]
- Makikallio AM, Makikallio TH, Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllylä VV. Heart rate dynamics predict poststroke mortality. *Neurology* 2004;62:1822–1826. [PubMed: 15159485]
- Martino TA, Tata N, Belsham DD, Chalmers J, Straume M, Lee P, Pribrag H, Khaper N, Liu PP, Dawood F, Backx PH, Ralph MR, Sole MJ. Disturbed diurnal rhythm alters gene expression and exacerbates cardiovascular disease with rescue by resynchronization. *Hypertension* 2007;49:1104–1113. [PubMed: 17339537]
- Merati G, Di Rienzo M, Parati G, Veicsteinas A, Castiglioni P. Assessment of the autonomic control of heart rate variability in healthy and spinal-cord injured subjects: Contribution of different complexity-based estimators. *IEEE Trans Biomed Eng* 2006;53:43–52. [PubMed: 16402602]
- Penev PD, Kolker DE, Zee PC, Turek FW. Chronic circadian desynchronization decreases the survival of animals with cardiomyopathic heart disease. *Am J Physiol* 1998;275:H2334–H2337. [PubMed: 9843836]
- Peng CK, Havlin S, Hausdorff JM, Mietus JE, Stanley HE, Goldberger AL. Fractal mechanisms and heart rate dynamics. Long-range correlations and their breakdown with disease. *J Electrocardiol* 1995;28 (Suppl):59–65. [PubMed: 8656130]
- Penttilä J, Helminen A, Jartti T, Kuusela T, Huikuri HV, Tulppo MP, Scheinin H. Effect of cardiac vagal outflow on complexity and fractal correlation properties of heart rate dynamics. *Auton Autacoid Pharmacol* 2003;23:173–179. [PubMed: 14690492]

- Perkiomaki JS, Zareba W, Daubert JP, Couderc JP, Corsello A, Kremer K. Fractal correlation properties of heart rate dynamics and adverse events in patients with implantable cardioverter-defibrillators. *Am J Cardiol* 2001;88:17–22. [PubMed: 11423052]
- Saleh MA, Winget CM. Effect of suprachiasmatic lesions on diurnal heart rate rhythm in the rat. *Physiol Behav* 1977;19:561–564. [PubMed: 565934]
- Scheer FA, Pirovano C, Van Someren EJ, Buijs RM. Environmental light and suprachiasmatic nucleus interact in the regulation of body temperature. *Neuroscience* 2005;132:465–477. [PubMed: 15802197]
- Scheer FA, Ter Horst GJ, Van der Vliet J, Buijs RM. Physiological and anatomic evidence for regulation of the heart by suprachiasmatic nucleus in rats. *Am J Physiol Heart Circ Physiol* 2001;280:H1391–H1399. [PubMed: 11179089]
- Schwartz WJ. Suprachiasmatic nucleus. *Curr Biol* 2002;12:R644. [PubMed: 12361580]
- Shlesinger, MF.; West, BJ. *Random Fluctuations and Pattern Growth: Experiments and Models*. Boston: Kluwer Academic Publishers; 1998.
- Stanley, HE. *Introduction to Phase Transitions and Critical Phenomena*. London: Oxford University Press; 1971.
- Warren WS, Champney TH, Cassone VM. The suprachiasmatic nucleus controls the circadian rhythm of heart rate via the sympathetic nervous system. *Physiol Behav* 1994;55:1091–1099. [PubMed: 8047576]

Figure 1.

Circadian rhythms of heart rate in rats are abolished by suprachiasmatic nucleus (SCN) lesion. (A) Ten-day continuous heart rate recordings of a representative control rat and a representative SCN-lesioned rat (SCNx) both throughout 12-h light/dark cycles (LD) and under constant darkness (DD). (B) The left panel shows power spectral densities of the individuals' heart rate recordings from A, and the right panel shows the same individuals' heart rate recordings averaged over the estimated circadian period (i.e., ~24 h) after aligning the data according to the onset of darkness (circadian time, CT = 0 h). Under the DD, circadian period in each control rat was estimated from rhythmicity in core body temperature, whereas in SCNx rats, in which circadian rhythmicity was eliminated, the average circadian period of all the control rats was used (i.e., 24.1 h). Under the LD, the circadian clock was synchronized to the 12:12 light/dark cycles with lights-on assigned ZT = 0 (Zeitgeber time), which corresponded to CT = 12 h. Because the DD protocol followed 12-h dark condition in the LD, the circadian time at the beginning of the DD was approximately 12 h. (C) The group average power spectral densities and average 24-h activity waveforms of control rats and SCNx rats. For better clarity and to avoid overlap, power spectral curves are vertically offset. Note that the abscissa of the power spectrum is a log scale with time (thus higher frequencies appear to the left of lower frequencies).

Figure 2.

Suprachiasmatic nucleus (SCN) lesion abolishes scale-invariant patterns of heart rate fluctuations at time scales above 3.6 h. (A) Correlation analysis in the heart rate recordings in representative individual control and SCNx rats (upper plots), and in the group averages (lower plots) during 12 h light/dark cycle (LD) and under constant darkness (DD). Data are shown on log-log plots. On the abscissa, n represents the time scale in hours. The detrended fluctuation functions $F(n)$ are vertically shifted for a better visualization of differences between control and SCNx rats. SCN lesioning had strikingly different effects at long time scales when compared with shorter time scales. The precise time scale at which this distinction occurred is better demonstrated in the derived plots in B, which represent the ratio of control/SCNx rats. There is a clear turning point in these ratios at a time scale of ~ 3.6 h for the detrended fluctuation function—see dotted vertical lines on each plot. Thus, we defined 2 time-scale regions for analysis: Region 1 is 16 min to 3.6 h (i.e., to the left of the dotted vertical line; indicated by exponent α_1) and region 2 is 3.6 to 24 h (i.e., to the right of the dotted vertical line; indicated by exponent α_2). These figures present the average scaling behavior across all time scales. It is also possible to examine variations in scaling behavior at short time scales, and elsewhere we report such variations across the circadian cycle (Hu et al., in press).

Figure 3.

Scale invariance in heart rate fluctuations and mean activity during inactive period in DD and LD protocols. (A) Similar scale invariance in heart rate fluctuations characterized by the scaling exponent during DD and LD protocols. (B) Significant higher mean activity level during DD protocols than during LD protocols. p values were obtained using analysis of variance with repeated measures. Error bars represent standard deviation.

Figure 4.

Scale invariance of heart rate fluctuations and activity fluctuations of control rats in DD and LD during active period (A) and inactive period (B). There was no significant correlation between cardiac scaling exponents and activity scaling exponents during both active period (DD: $R^2 = 0.043$, $p = 0.25$; LD: $R^2 = 0.051$, $p = 0.21$) and inactive period (DD: $R^2 = 0.005$, $p = 0.70$; LD: $R^2 = 0.031$, $p = 0.33$).

Figure 5.

Schematic diagram of the contributions of the suprachiasmatic nucleus (SCN) to the complex statistical features in heart rate fluctuations. Control rats exhibit virtually identical scale-invariant patterns of heart rate fluctuations across a time scale from minutes up to 24 h. This scale-invariant pattern is very robust, being unaffected by the environmental light/dark cycle. Comparison of results of control rats (left panels) and SCNx rats (right panels) demonstrates that the SCN not only drives the circadian waveform in mean heart rate, but it is also required for the normal scale-invariant regulation of heart rate fluctuations particularly from 3.6 to ~24 h (i.e., rather than solely at a period of ~24 h). We speculate that there must exist an intrinsic multiscale cardiac control system that orchestrates the short- and long-term influences on heart rate to produce an overall scale-invariant pattern, perhaps via coupled cardiac control nodes operating at different time scales, and that the SCN is one of the important nodes of this multiscale regulation (left panel; upper plot, where the SCN is embedded within a multiscale regulator of heart rate; in this simplified diagram, only 1 other control node is depicted, however, there could be multiple other control nodes next to the SCN). Our results also indicate the existence of non-SCN-related multiscale heart rate regulation that is primarily responsible for the stable scale-invariant patterns of heart rate at time scales from minutes to 3.6 h.