Time Series Analysis of Heartbeat-Interval at the Subjects Ranging from Crustacean Animal to Human

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ABSTRACT

The aim of our study was to quantify the condition of the heart: sick or not in numerical order. In the present study, we focused attention on the period-2 heartbeat. "Alternans" is an arrhythmia exhibiting alternating amplitude/interval from beat to beat on the electrocardiogram and was first described in 1872 by Traube. Recently alternans was finally recognized as the harbinger of a cardiac disease, when an ischemic heart exhibited alternans. The pattern, alternans, arises spontaneously. As-yet-unidentified mechanisms must contribute. In animal models we detected alternans at various experimental conditions, including the heart under emotional stress and the heart of a dying specimen. We have tested the detrended fluctuation analysis (DFA) on alternans and revealed that in both, animal models and humans, alternans rhythm lowers the scaling exponent that was computed by the DFA. We concluded that the scaling exponent can reflect a risk for the "failing" heart, especially when the low scaling exponent and alternans are concurrently present.

Keywords: heartbeat, fuluctuation, DFA, animal model, alternans rhythm.

1. INTRODUCTION

Japanese persimmon trees bear rich fruits every other year. Atmospheric oxygen on the earth has bistability [1]. Period-2 is an intriguing rhythm in nature. The cardiac “alternans” is another period-2 phenomena. In cardiac period-2, the heartbeat is alternating the amplitude/interval from beat to beat. It can be seen on the electrocardiogram (EKG). Alternans has remained an electrocardiographic curiosity for more than three quarters of a century [2, 3]. To date, alternans is recognized as a marker for patients at an increased risk of sudden cardiac death [2, 3, 4, 5, 6,7].

We have been studying neurobiology of crustacean cardio-vascular system. In our physiological experiments on the hearts in the 1980’s, we have noticed that alternans is frequently observable with the “isolated” hearts (Note; the heart sooner or later dies in the experimental dish). We soon realized that it is a sign of future cardiac cessation. Nowadays, some authors believe that it is the harbinger for sudden death [2, 6]. So, we came back to the crustacean physiology. As-yet-unidentified mechanisms must contribute to this abnormal heartbeat. Details of alternans have not been studied in crustaceans. But, we considered that we may study this intriguing rhythm by the detrended fluctuation analysis (DFA), since we have demonstrated that the DFA can distinguish a normal heart (intact heart) from an unhealthy heart (isolated heart) in animal models [8]. In the present investigation, we describe that period-2, alternans, lowered scaling exponent.

2. MATERIALS AND METHODS

DFA Methods: Background

The DFA is based on the concept of “scaling” and “universality” [9]. It is a method to understand a “critical” phenomena [9, 10, 11]. Systems near critical points exhibit self-similar properties, and therefore, in physics, they are invariant under a transformation of scale.

Stanley and colleagues have considered that the heartbeat fluctuation is a phenomenon, which has the property of scaling. They first applied the concept to a biological data, the DNA and the EKG in the late 80’s to early 90’s [10, 11]. They emphasized on its potential utility in life science [11]. Technologically, it seems not matured, but practical use of nonlinear technology is widely accepted and increasingly advancing.

DFA Methods
We made our own programs for measuring beat-to-beat intervals, and for calculating the approximate scaling exponent of the interval time series (K. Tanaka [13]). Those DFA-computation methods have already been explained elsewhere [12, 13]

Heartbeat recording
From human subjects we used the finger pulse recording with a Piezo-crystal mechanic-electric sensor, connected to a Power Lab System (AD Instruments, Australia). From model animals we used electrophysiological recording with two metal electrodes implanted to the dorsal carapace (pictures in Figs. 1 and 3). The attached electrodes often stayed on animal carapace until ecdysis.

Volunteers and ethics
Human subjects were selected from colleagues in our university, volunteers who were voluntarily visited us desiring their heart to be checked. All subjects were treated as per the ethical control regulations of our university, Tokyo Metropolitan University.

Model animals
It is very important that animal models are healthy before an investigation. We confirmed that all animals used were naturally healthy before starting any experiments. We observed with our own eyes when we captured all specimens from a natural habitat by ourselves. The EKG recordings from crustacean model animals were done by implanted permanent metal electrodes, which are connected to the Power Lab System. By this recording, animals were usually walked around in the container.

3. RESULTS AND DISCUSSION

It is known that the human heart rate goes up to over 200 beats per min (BPM), when life comes to an end. During the period through the brain death, a figure data is shown in a reference (see Fig. 1 of [14]).

In an animal model, an increase of heart rate during the dying period was observable, for example, crustaceans (Fig. 1) and insects (data not shown). This demonstrates a strong resemblance of a cardiac control mechanism between lower animals and humans. The heart of those animals is innervated from the autonomic nerve system. Evolutionally, this similarity was noticed (see, "Natural selection 150 years on", Nature insight Feb 12, 2009 pp808-811). There is another reason to use lower animals in medical investigations. Crab/shrimp are our foods. Ethics is of course a big requisition. Furthermore, we nowadays know Gehring's discovery of a gene, named homeobox: To our surprise at that time of his discovery, an identical gene named "pax-6" was found to work both, in fly's eyes and mouse's eyes at an embryonic stage for developing an optical sensory organ [15]. Fundamentally creatures are all the same in basic physiology. Both the crustaceans and humans have "the autonomic nerves," i.e., acceleratory and inhibitory cardio-regulatory nerves.

EKG from a dying crab/shrimp exhibited alternans (Fig. 1B). This alternans was followed by a period of high-rate heartbeats (Fig. 1C), which is an indication of terminal condition. Alternans is thereby the harbinger of death in crustacean animals. Interestingly no alternans is seen at the terminal condition (Fig. 1C).

The DFA of alternans revealed that the alternans exhibits a low approximate scaling exponent (see below). Alternans and low exponents would be a sign of illness. We have long noticed that the isolated heart, which can repeat contractions for hours in a dish, often exhibits alternans (Fig. 2B1). The DFA revealed that the scaling exponent of alternans is low, i.e., slope is far lower than one (Fig. 2B2). We tested another three-isolated hearts of this lobster species, all of which exhibited alternans (data not shown), and we found that the scaling exponent of the alternans' heart was low. A healthy lobster, however, exhibits a normal scaling exponent (see Figs. 2A1 and 2A2).

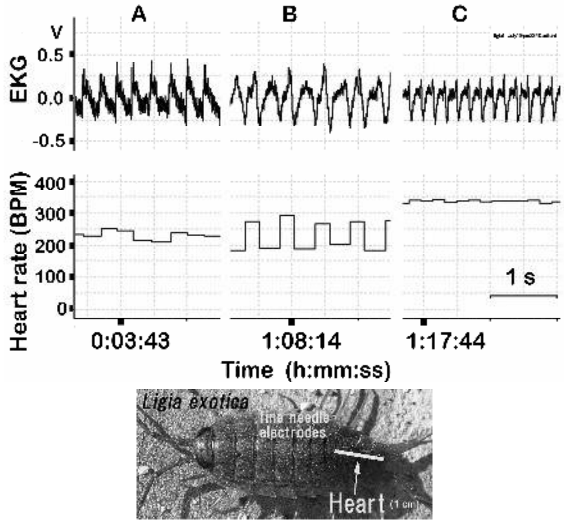

Figure 1. EKG from a dying isopod crustacean, *Ligia exotica*. (A) A recording started at time zero. The base line heart rate is about 250 beat per minute. (B) One hour after (A), an irregular rate and alternans can be seen. (C) About 1.2 hours after (A), no alternans is seen. The heart rate increased to about 350 beats per minute. This crab died 1.3 hours after the recording (A).

We once drew a conclusion that freely moving animals without stress do not exhibit alternams and they exhibit a normal scaling exponent. However, further studies uncovered that a crayfish can spontaneously exhibit alternans when it had an emotional arousal (Fig. 3). This alternans is apparently not dying. We finally confirmed alternans is recorded especially at the top speed of its racing heartbeat (Fig. 3). So far we do not know the mechanism of generation of alternals. It seems that alternans comes out from complex interactions between the heart and brain, such as psychological excitement. This type of alternans does not last for long, 30 second at the most (Fig. 3). We cannot apply the DFA to such an interesting psychological or emotional phenomena, because the DFA needs about 2000 heartbeats. If it could last for 5 minutes, we could do calculate approximate scaling exponent of alternans, and we did it (Fig. 2).

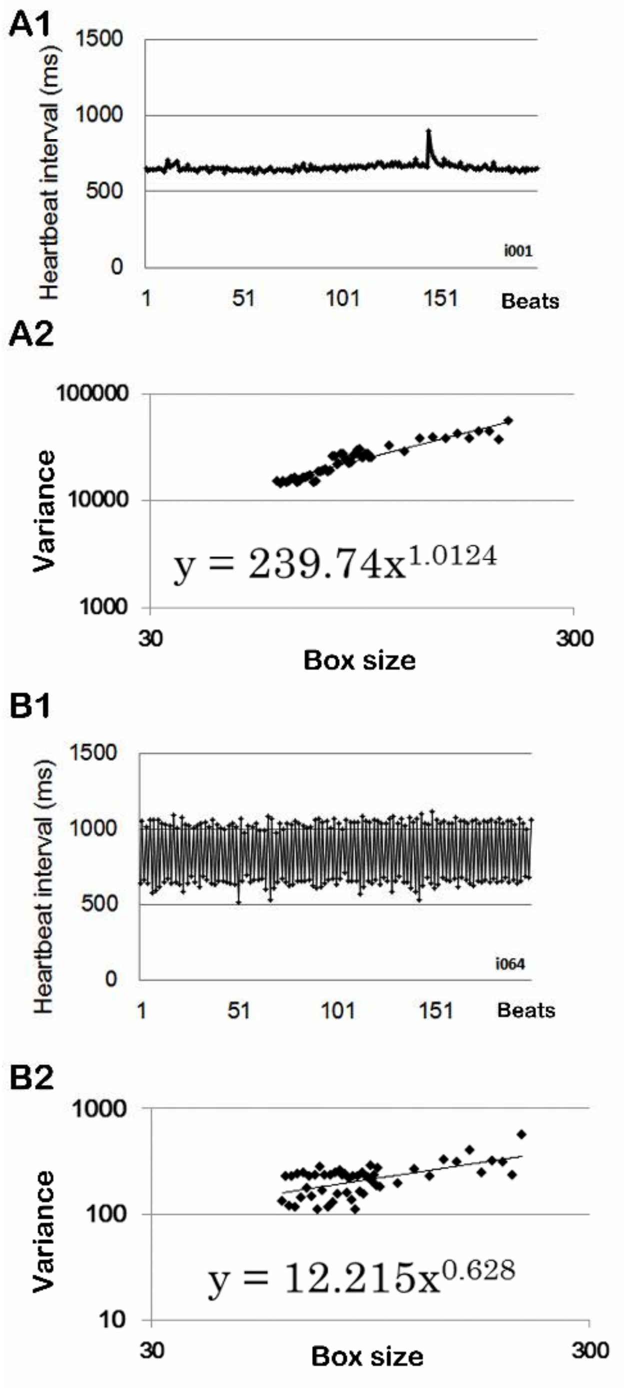

Figure 2. Intact (A) and isolated (B) heart of a spiny lobster, *Panulirus japonicus*. A1 and B1, 100 heartbeats. A2 and B2, DFA computation. A2, Intact heart exhibited a scaling exponent 1.0124. No alternans appeared (see A1). B2, Alternans appeared here all the way down from the first beat to 4000th beat (not shown all). The scaling exponent was found to be low, 0.628, which was computed at box size 60-210.

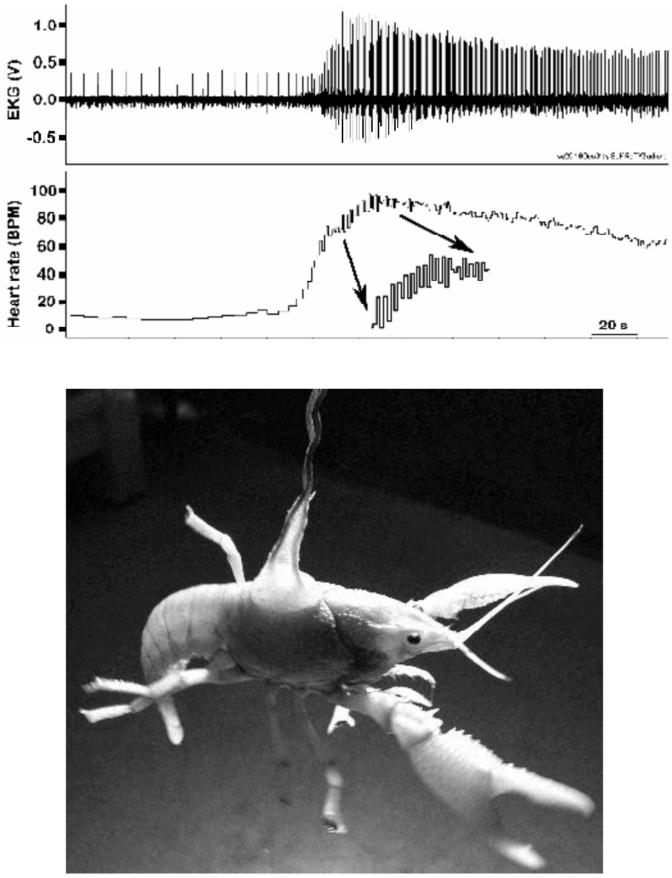

Figure 3. Crayfish *Procambarus clarkii* exhibits alternans. It occurs at a top speed of a cardiac acceleration. This occurs spontaneously when the animal was in the shelter. Upper, EKG. Lower, Heart rate in beat per min. Inset, Enlargement of Alternals. Both amplitudes alternans and intervals alternans can be seen (see A). Picture: Crayfish hanging in the air with EKGs recording wires.

Finally, we studied the human alternans. The finger pulse of a volunteer was tested (Figs. 4 and 5). Similar to the models, human alternans exhibited a low exponent (Fig. 6). This subject, a 65 years old female is physically weak and she cannot walk a long distance. However, she talked with an energetic attitude. She was at first nervous because of us, but finally she got accustomed to our finger pulse testing task, and then she became relaxed. Hours later, we were surprised to note that her alternans decreased in numbers. The heart reflects the mind. We observed that alternans is coupled with the psychological condition, probably with an impulse discharge frequency of the autonomic nervous system. This is fundamentally similar to the animal models.

Alternans is believed to be the harbinger for a sudden death [2, 6]. A low scaling exponent accompanied with alternans seems to be a serious case. In contrast, it is believed that healthy human hearts exhibit a scaling exponent of 1.0 [11]. We obtained the same results (data not shown).

Figure 7 shows an example of alternans in which the subject's heartbeats show a period-2 rhythm (Fig. 7A). We met him in 2007 at an exhibition called Innovation Japan 2007. At that time he at first told us that he knew that his heart was not normal and he regularly went to see a doctor. He visited us because we presented our DFA method at the exhibition. We recorded his heartbeat (Fig. 7A). His scaling exponent in September 2007 was 0.6709 (see Figure 7B and 7C). We explained to him that he had alternans, and what is alternans as far as we knew.

In September 2008 and 2009, we returned to the exhibition. We did not expect he visited us again but he came. We recorded his heartbeat and calculated his scaling exponent. Especially in September 2009, to our surprise, the alternans was almost gone, and his scaling exponent increased than in 2007 (see Fig. 8, the scaling exponent was 0.733). He said that since learning the results shown in Fig. 7 in 2007, he had been walking to work instead of driving, every day. In September 2010, we returned to the exhibition and he visited us. He was mandatory retired from work in 2009, and he said he is staying at home. Figure 9 shows that an increase of the scaling exponent from 2007 to 2009 stopped in 2010 because of retirement.

His scaling exponents were compared in Fig. 9. Three different DFA computations at different box size are shown. Years 2007 - 2010 are compared. Figure 9 summarizes that his scaling exponents were improved although retirement stopped it. When he was working at Toshiba Co. Ltd, the exponents shifted to the direction toward to the good health state which is ultimately 1.0. We would say: "Efforts bear fruit." "DFA is useful."

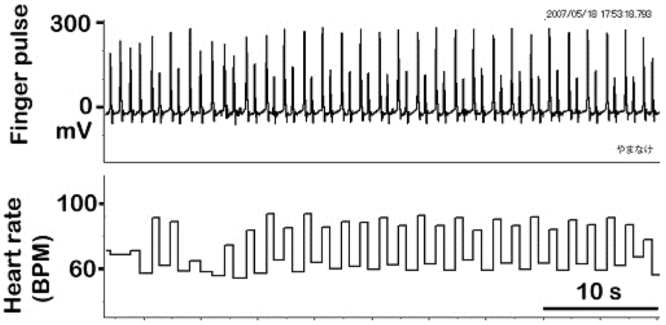

Figure 4. Human alternans. A volunteer woman age 65. Upper trace, recording of finger pulses. Lower trace, heart rate.

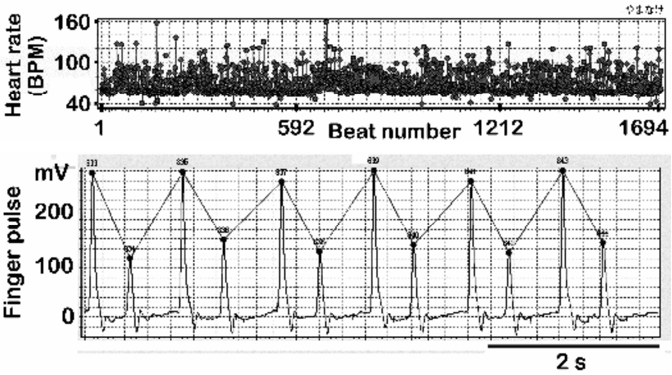

Figure 5. Human alternans. The same volunteer woman shown in Fig. 4. Upper trace, Time series, 1701 beats. Lower trace, Example recording, beat number 833 – 844. Both amplitudes alternans and intervals alternans can be seen.

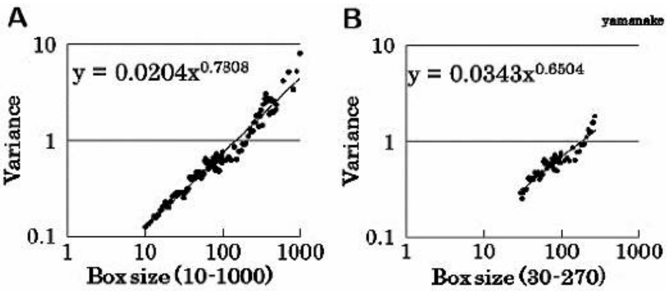

Figure 6. Result of the DFA of human alternans shown in Figs. 4 and 5. A, Box size, 10-1000. B, Box size, 30-270. Straight lines represent a slope obtained from different box-size-length. Theoretically, the slop determines the approximate scaling exponent. The 45-degree slope (not shown here) gives the scaling exponent 1.0 which represents that the heart is totally healthy. The alternans significantly lowers the scaling exponent in human heart as well as in crabs.

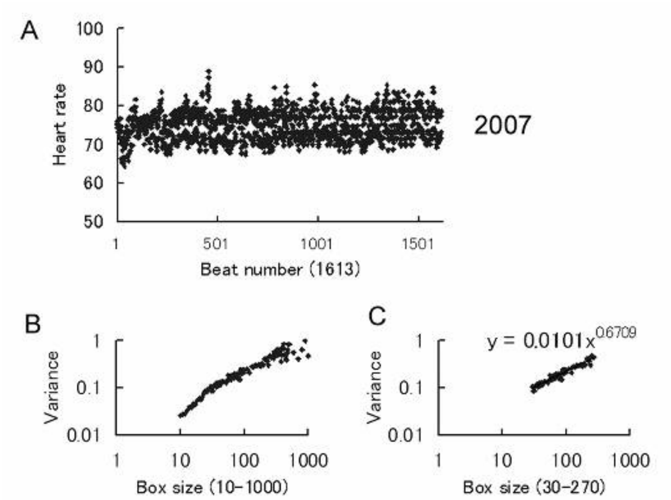

Figure 7. DFA of alternans. Recorded in September 2007 in Tokyo in his age 60s.

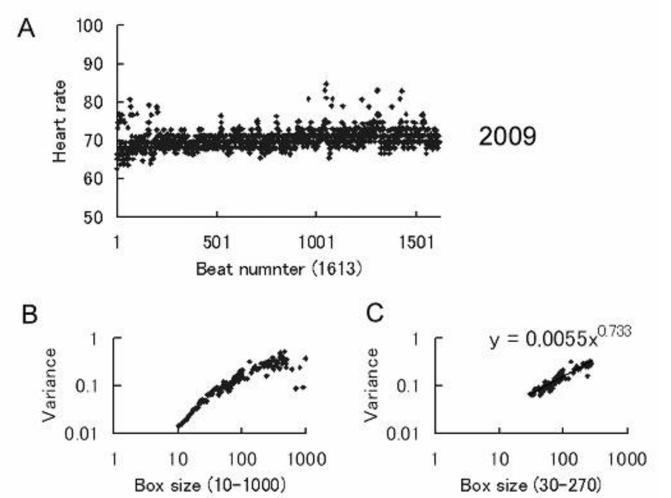

Figure 8. DFA of alternans. Recorded again in September 2009 in Tokyo.

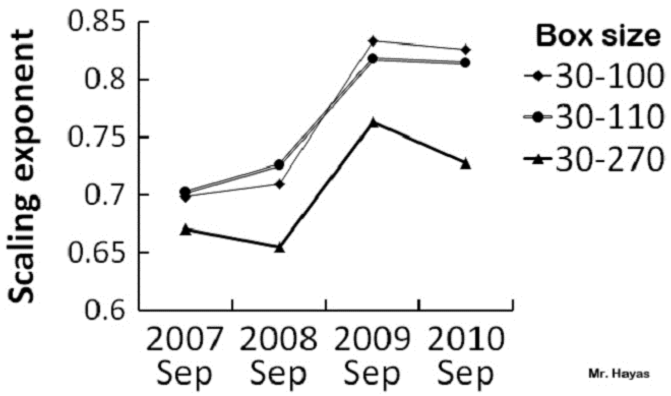

Figure 9. Comparison of the scaling exponents at different box size. Computed from the data from the subject shown in Figures 7 and 8.

A real time observation of both, EKG-signal and biological condition of a specimen, is important to interpret the physiological meaning of the scaling exponent. We did all investigations in front of us together with the on-line EKG observation. We thus were able to interpret/speculate the direct relationship between EKG-changes to behavioral changes. It seems that, until recently, clinicians took recordings and physicists analyzed the recordings. We performed both, recordings and analysis by the same scientists. This is one important point of advantage in this study, compared with the previous DFA report.

Other important points of our present study are that we made our own PC program (program by K. Tanaka [13]), which assisted the accuracy of the peak-identification of heartbeats, and then the calculation of the scaling exponent. Furthermore, supported by the real time observation, we were able to distinguish numerically and quantitatively normal hearts from abnormal hearts. It is said that alternans is the harbinger of a sudden death of humans. That was true in dying models. However, alternans was detectable everywhere in models; for example, during emotional changes (Fig. 3). Therefore stressful psychological circumstances may invoke autonomic acceleratory commands in the brain and then the commands finally trigger alternans in the heart.

4. CONCLUSION

We have previously made an automated DFA computation program which enabled us to perform variety of analysis on the heartbeat obtained both from model animals and human subjects. Using the original program, we were able to determine fine or poor health for each subjects: An appropriate box size is about 30-270 beats. Finally, we reached the conclusion that alternans lowers the approximate scaling exponent. Furthermore, alternans appears not only in dying conditions but also in emotionally stressful conditions.

5. ACKNOWLEDGEMENT

This research was supported by a Grant-in-Aid for Scientific Research No. 23500524 to TY. We thank DVX Co. Ltd. for financial support for the research.

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