Alternans Lowers the Scaling Exponent of Heartbeat Fluctuation Dynamics in Animal Models and Humans

Toru Yazawa, Katsunori Tanaka, Atsushi Kato, Tomoyuki Nagaoka, Tomoo Katsuyama

***Abstract*—"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. In animal models we detected alternans at various experimental conditions, including the heart with injury, 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.**

***Index Terms*—Alternans Heartbeat, Animal models, Crustaceans, DFA.**

I. Introduction

A persimmon tree bears rich fruits every other year. Atmospheric oxygen on the earth has bistability [1]. Period-2 is an intriguing rhythm in nature's environment. 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]. Recently, alternans is recognized as a marker for patients at an increased risk of sudden cardiac death [2], [3], [4], [5], [6]. In our physiological classical experiments on the crustaceans 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. Details of alternans have not been studied in crustaceans. But, we considered that, since we have demonstrated that the detrended fluctuation analysis (DFA) can distinguish a normal heart (intact heart) from an unhealthy heart (isolated heart) in animal models [7], we may study this intriguing rhythm by the DFA. We here describe that alternans and lowered scaling exponent occurred concurrently. This finding may contribute to the advance in management of the dysfunction of a complex cardiovascular disease.

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II. Procedure

A. 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. This is the property of scaling. And this is known as a "critical" phenomena.

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 nonlinear technology is accepted and increasingly advancing.

B. 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. Those DFA-computation methods have already been explained elsewhere [12]. We describe it here for biological scientists who have no background of physics.

Firstly, we recorded the heartbeat, for about 10 to 50 minutes. Usually we recorded pulses for about 50 minutes at a single testing, because 3,000 beats were necessary for our calculation of an approximate scaling exponent. We recorded an EKG or finger pressure pulses. (We have innovated: Based on a brief-period data, lasting for only 5 minutes, we calculate the approximate scaling exponent. We do not mention it here.)

Secondly, pulse peaks $\{P_i\}$ were captured by our own program. By eye-observation on the PC screen with our own program, all real peaks were identified and noise peaks were removed. Its entire beat was confirmed by our eyes though it is a time consuming task. Experiences on neurobiology and cardiac animal physiology were sometimes necessary when determining whether a spike-pulse is a cardiac signal or a noise.

Thirdly, using our own program, intervals of the heartbeat $\{I_i\}$, such as the R-R intervals of an EKG, were calculated, which is defined as:

$$\{P_{i+1} - P_i\} = \{I_i\} \tag{1}$$

Fourth, the mean-interval was calculated, which is defined as:

$$< I > \tag{2}$$

Fifth, the fluctuation value was calculated by removing a mean value from each interval data, which is defined as:

$$I_i - < I > \tag{3}$$

Sixth, a set of data $\{B_i\}$ upon which we do the DFA was obtained by adding each value derived from the equation (3), which is defined as:

(4)

$$B_i = \sum_{k=0}^{i} (I_k - < I >)$$

Here the maximum number of i is the total number of the data point, i.e., total number of peaks in a recording. In the next step, we determine a box size, τ (*TAU*), which represents the number of beats in a box, and which can range from 1 to maximum. Maximum *TAU* can be the total number of heartbeats to be studied. For the efficient and reliable calculation of the approximate scaling exponent in our program, we confirmed by test analysis that the number of total heartbeats is hopefully greater than 3,000. If *TAU* is 300, for example, we can obtain 10 boxes.

Seventh, we calculate the variance which is defined as:

$$F^2(\tau) = < B_{i+\tau} - B_i > \tag{5}$$

Here we adopted a method for "standard deviation analysis." This method is probably the most natural method of variance detection [see 18]. Mathematically, this is a known method for studying "random walk" time-series. Peng et al. [10] used a different idea than ours. As mentioned above, they are considering that the behavior of the heartbeat fluctuation is a phenomenon belonging to the "critical" phenomena. A "critical" phenomenon is involved in a "Random-walk" phenomenon. Our consideration is that the behavior of heartbeat fluctuation is a phenomenon involved in a "random walk" type phenomenon. Peng et al. [10] used much a stricter concept than ours. There is no mathematical proof whether Peng's or ours is feasible for the heartbeat analysis, since the reality of the complex system is still under study. Probably the important point will be if the heartbeat fluctuation is a "critical" phenomenon or not. What we wondered is that the physiological *homeostasis* is a "critical" phenomena. We simply prefer a tangible method in technology to uncover "something" is wrong with the heart instead of what is the causality of a failing heart. So far, no one can deny that the heartbeat fluctuation belongs to the "critical" phenomena, but also there is no proof for that. We chose technically "random walk." The heartbeat fluctuation is transformed to the "random walk." We made random walk time series from the data by the equation (4).

Finally, eighth, we plotted a variance against the box size. Then the scaling exponent is calculated, by seeing in the slope portrayal. Most of computations mentioned above, which are necessary to obtain the scaling exponent, are automated. The automatic program relatively quickly gives us an approximate scaling exponent. So, although we cannot have a critical discussion whether or not the exponent is precisely 1.0 or not, our automatic program is helpful and reliable to distinguish a normal state of heart (scaling exponent exhibits near 1.0) from a sick state of heart (high or low exponent). So, in this report, we mention the three categories in differentiation; normal, high, and low.

C. EKG and finger pulse

From human subjects we mostly used the finger pulse recording with a Piezo-crystal mechanic-electric sensor, connected to a Power Lab System (AD Instruments, Australia). 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.

D. Model animals

It is very important that animal models are healthy before an investigation. We must confirm that all animals used are naturally healthy before starting any experiments. We observed with our own eyes. Therefore, we captured all specimens from a natural habitat by ourselves.

III. RESULTS

It is known that the human heart rate goes up to over 200 beats per min. when life comes to an end (Dr. Umeda, Tokyo Univ. Med.; Dr. Shimoda, Tokyo Women Med. Univ., personal communication). During the period through the brain death, a similar data is shown in a reference (see Figure 1 of [13]).

In an animal model, an increase of heart beats during the dying period was observable (Fig. 1). Here, the heart rate was normally about 200. The body length is 3 cm. A small animal's heart rate is relatively high. At terminal condition (see N, O, and P in Fig. 1), the heart rate attained over 300 beats. We consider that this demonstrates a strong resemblance of a cardiac control mechanism between lower animals and humans.

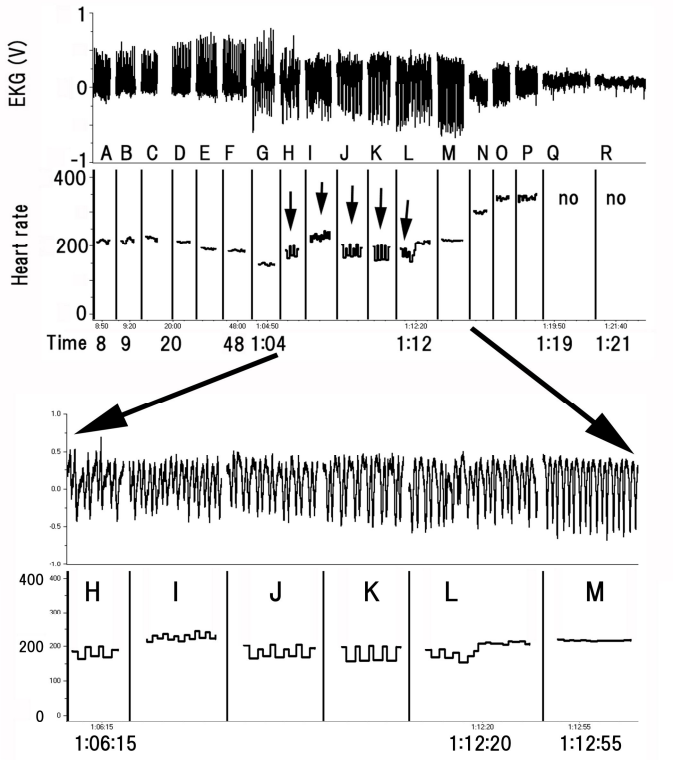

Fig. 1. EKG and heart rate of a dying crustacean, isopods, *Ligia exotica*. Two metal electrodes, 200 micrometer in diameter, were placed on the heart by penetrating them through the dorsal carapace. A sticky tape on a cardboard immobilized the animal. Records are shown intermittently for about one hour and 20 minutes. From H to M, the EKG and heart rates are enlarged. Small 5 arrows indicate alternans, which is observable at H-L. From Q to R, *no* means that the computation failed due to a small size signal with a sporadically appearance.

Evolutionally, this similarity (a general idea that animals evolved from a common ancestor) was first noticed by a German scientist, who noted: "Biogenetische Grunderegel" ("Recapitulation theory" by Ernst Heinrich Philipp August Haeckel). There is another reason to use lower animals. Ethics is of course a big requisition. But, we know Gehring's discovery of a gene, named *homeobox*: To our surprise at that time, 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 [14], [15]. In 2007, further strong evidence has been presented with a new data for the origin of the central nervous system: The role of genes which patterns the nervous system in embryos of choldates (like humans) and annelids (a lower animal) are surprisingly similar and the mechanism is inherited almost unchanged from lower animals to higher animals through a long period of geology [16], [17].

In this isopod specimen (Fig. 1), interestingly, a significant alternans is seen when they are dying (H, I, J, and K, Fig. 1). Its alternans lasted for not long; we did not perform the DFA on this data.

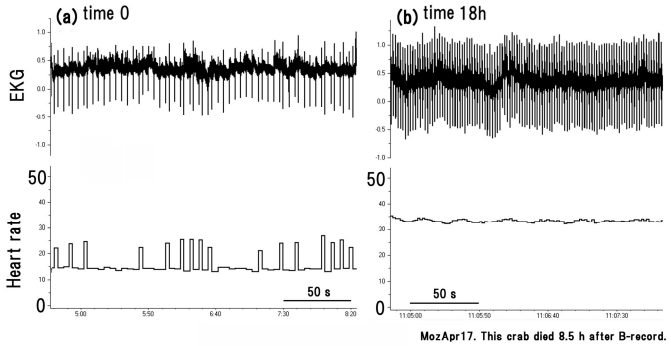

Fig. 2. EKG from a dying Mitten crab, *Eriocheir japonicus*. (a) A recording started at time zero. An irregular rate and alternans can be seen. The base line heart rate is about 15 beat per minute. (b) 18 hours after *(a)*, no alternans is seen. The heart rate increased to about 35 beats per minute. This crab died 8.5 hours after the recording *(b)*.

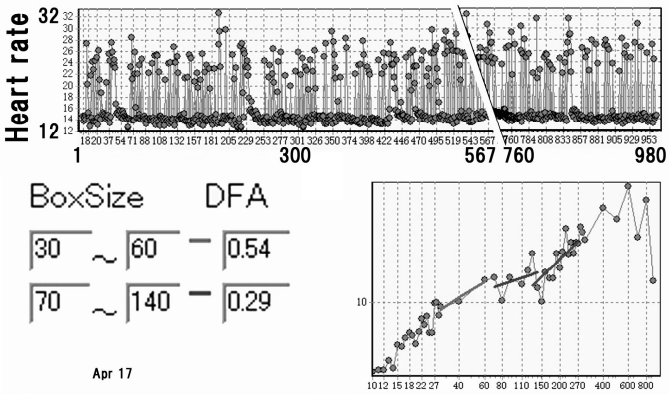

Fig. 3. Mitten crab DFA. The same crab shown in Fig. 2. About 980 beats for the DFA; the middle part was omitted. The approximate scaling exponent for alternans was low. Short-term box-size "30 beat ~ 60 beat" and "70 beat ~ 140 beat" were calculated.

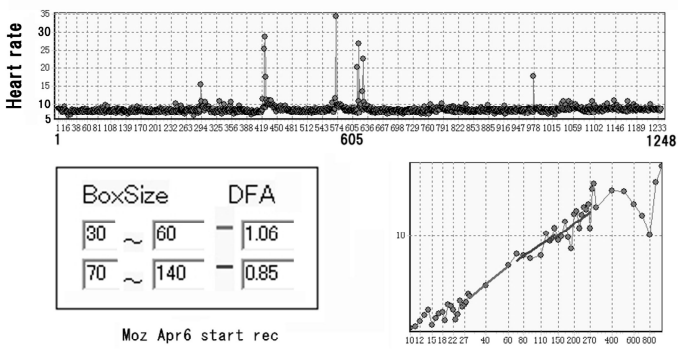

Fig. 4. Mitten crab DFA. The same crab shown in Figs. 2 and 3. But the recording was immediately after the specimen was captured. The approximate scaling exponent was not low but ~1.0 (cf., Fig. 3). The crab's heart seems to be normal on the first day of the experiment.

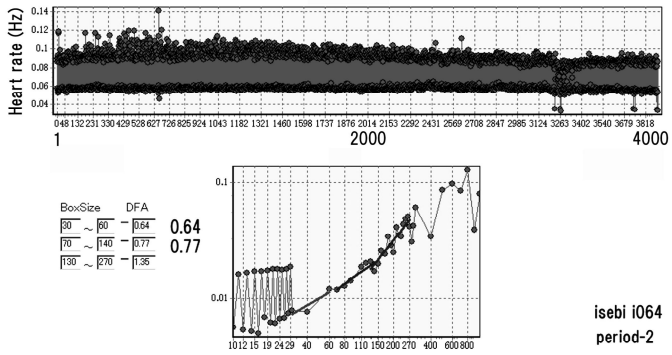

Fig. 5. Isolated heart of a spiny lobster, *Panulirus japonicus*. Alternans appeared here all the way down from the first beat to 4000th beat. The scaling exponent was found to be low.

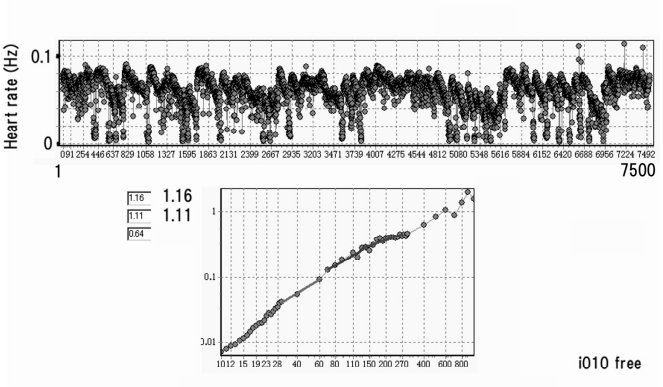

Fig. 6. The DFA of an intact heart of a spiny lobster, *Panulirus japoniculs*. No alternans appeared. The heart rate (shown in Hz) frequently dropped down, so-called bradycardia. This is well known in normal crabs and lobsters, first reported by Wilkens and McMahon at the Calgary University [19]. The present DFA revealed that the scaling exponent is normal when the lobster is freely moving in the tank.

EKG from a dying crab also exhibited alternans. Alternans appeared intermittently but very densely (Fig. 2a, Fig 3). This alternans was followed by a period of high-rate heartbeats (Fig. 2b). The DFA of alternans revealed that the alternans exhibits a low approximate scaling exponent (Fig. 3). As far as we know, this is the first report of DFA on alternans. It is noteworthy that the crab has had a normal, approximate scaling exponent 11 days ago (Fig. 4) when an EKG recording was first done, right after its collection in the South Pacific, on Bonin Island. Therefore, alternans and low exponents would be a sign of illness.

We noticed that the isolated heart, which can repeat contractions for hours in a dish, often exhibits alternans (Fig. 5). The DFA again revealed that the scaling exponent of alternans is low (Fig. 5). We therefore tested another three-isolated hearts of this lobster species, all of which exhibited more or less alternans (data not shown), and we found out that the scaling exponent of the alternans' heart was low. A healthy lobster, however, exhibits a normal scaling exponent (Fig. 6).

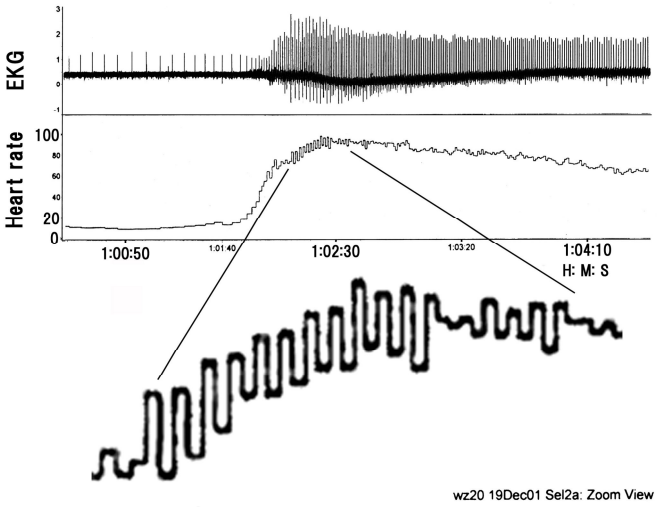

Fig. 7. EKG and heart rate recordings from a freely moving mutant-white crayfish, *Procambarus clarkii*. An arousal from sleep might happen. Alternans can be seen at a rising phase of a heart rate tachogram.

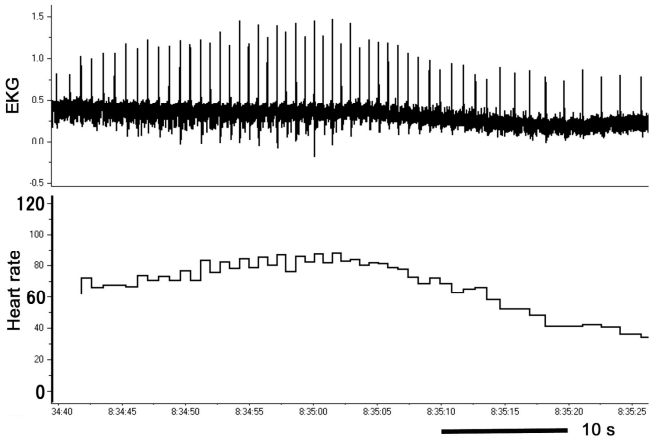

Fig. 8. Crayfish exhibits alternans. It occurs at a top speed of a cardiac acceleration. This occurs spontaneously when the animal was in the shelter.

We once drew a conclusion that freely moving animals without stress exhibit a normal scaling exponent. However, further studies uncovered a contradictory phenomenon. A crayfish spontaneously exhibited alternans when it had an emotional arousal (Fig. 7). We recorded alternans from a crayfish, which was apparently not dying. Alternans is recorded especially at the top speed of its racing heartbeat (Fig. 8). So far we do not know the mechanism. However, it seems that alternans comes out from complex interactions between the heart and brain, such as psychological excitement. Since this type of alternans does not last for long, 20 second at the most, we cannot apply the DFA to such an interesting psychological or emotional phenomena. If it could last for 5 minutes, we could do calculate approximate scaling exponent.

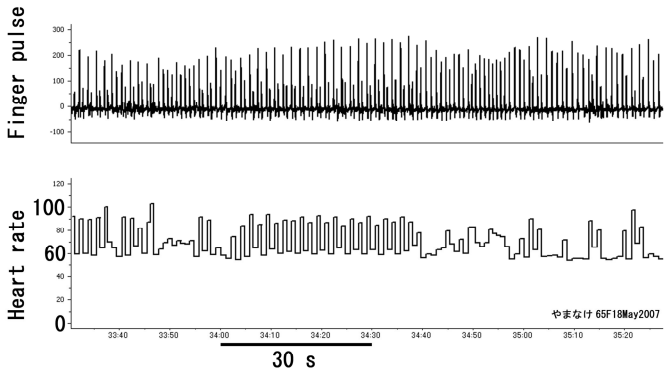

Fig. 9. Human alternans. A volunteer woman age 65. Upper trace, recording of finger pulses. Lower trace, heart rate. Both amplitudes alternans and intervals alternans can be seen.

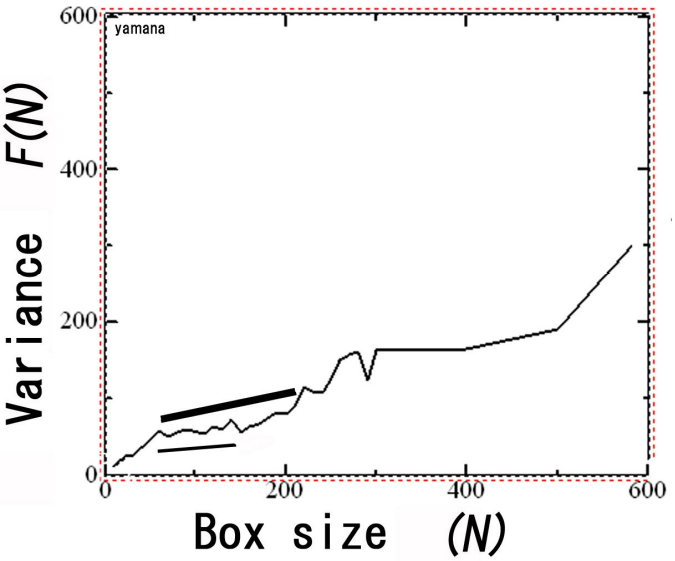

Fig. 10. Result of the DFA of human alternans shown in Fig. 9. Two thick and thin straight lines represent a slope obtained from different box-size-length. Theoretically, the slop determines the approximate scaling exponent. The 45-degree slope (not shown here) gives the scaling exponent 1.0 which represents that the heart is totally healthy. The other two lines, shown in this graph, are obviously less steep than the 45-degree slope. This argument draws a conclusion: The alternans significantly lowers the scaling exponent.

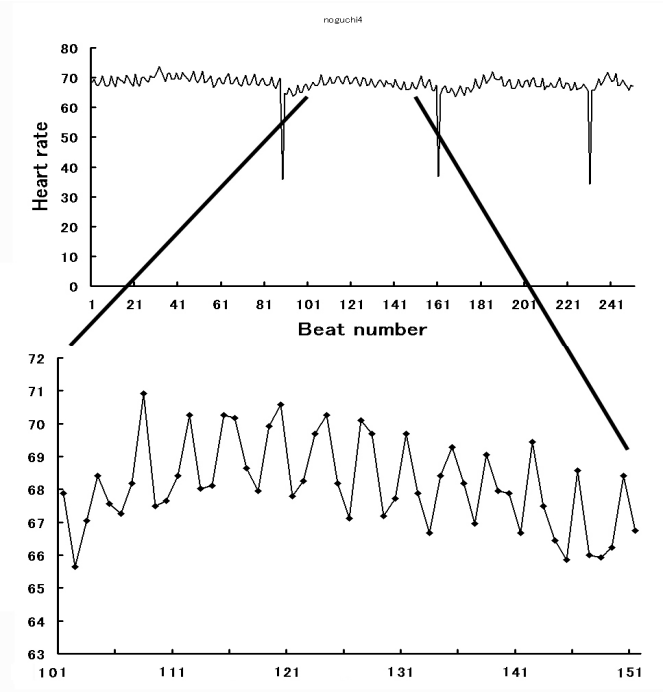

Fig. 11. An abnormally periodic heartbeat but no alternans. Mr. N., Age 75, a healthy looking man. He said: "Recent check ups revealed every thing is fine." "Quite normal except for my age" he added. He is involved very actively in teaching, in his profession.

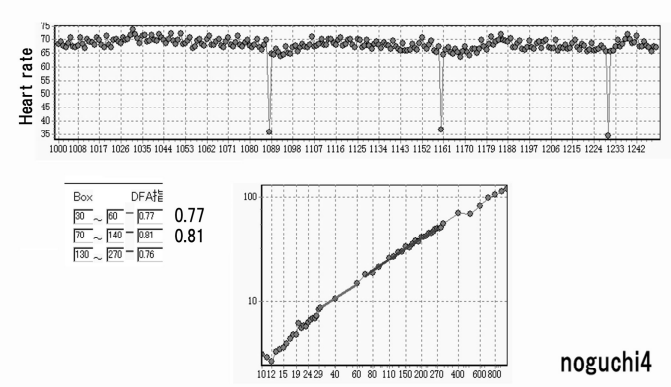

Fig. 12. A low scaling exponent of non-alternans people. The DFA of Mr. N's heart (shown in Fig. 11). Probably due to an abnormal periodicity.

Finally, we studied the human heart beat. The finger pulse of a volunteer was tested (Figs. 9 and 10). Similar to the models, human alternans exhibited a low exponent (Fig. 9). 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 (we did not realize it and even she herself didn't notice it), 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 crayfish models in Figs. 7 and 8.

It is known that healthy human hearts exhibit a scaling exponent of 1.0 [11]. Our analysis revealed the same results (data not shown, age 9 to 82, about 30 subjects). We encountered a healthy but interesting heart chart (Fig. 11). This heart is periodically oscillating. Skipped beats (arrhythmia) were rarely observable; here we selected three skipped beats for presentation. We applied the DFA to this data. Abnormal periodicity may lower the scaling exponent (Fig. 12), as alternans does (Figs. 9 and 10). This example (Figs. 11 and 12) implies "periodicity" lowers the scaling exponent. Alternans is believed to be the harbinger for a sudden death [2], [6]. The person, shown in Figs. 11 and 12, has no alternans. He is apparently healthy because we have frequently checked his heartbeat for more than 4 years. Periodicity and alternans are not the same. A low scaling exponent accompanied with alternans seems to be a serious case.

IV. Discussion

Usually the DFA necessitates a long heartbeat recording. A 24 hours recording is served for that purpose. However, a real time observation of both, EKG-signal and biological condition of a specimen, is also important to interpret the physiological meaning of the scaling exponent. We did all recordings 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, 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. Our DFA program shortened the period length of time-consuming analysis. We are presently developing a much simpler program for biologists who have no physical training. The new method freed us from complicated PC tasks before obtaining the result of a calculation of the scaling exponent. We can concentrate more on physiology instead of physics. As a result, we can handle many data, sampled from various models.

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 (Figs. 7 and 8). Therefore stressful psychological circumstances may invoke autonomic acceleratory commands in the brain and then the commands finally trigger alternans in the heart. This is a hypothesis. If problems exist in this consideration, that will be the number of specimens or subjects. This will be solved by further studies in the future.

Concluding remarks: Alternans lowers the approximate scaling exponent. Alternans appears not only in dying conditions but also in emotionally stressful conditions.

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