

DFA on Cardiac Rhythm: Fluctuation of the Heartbeat Interval Contain Useful Information for the Risk of Mortality in Both, Animal Models and Humans

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ABSTRACT

We analyzed the heartbeat interval to test the possibility that the detrended fluctuation analysis (DFA) distinguishes a sick condition from a healthy condition of the cardiac control network. The healthy heart exhibited exponents ranging from 0.8 to 1.0 in both, animal models and humans. In the sick animal models, the exponents declined with an approaching very low range leading to a natural death (~0.6 in the end). Other models, which had a myocardial injury, exhibited extremely high exponents (~1.4). The high exponent was maintained until they died. Human arrhythmic hearts exhibited low exponent (~0.7). A human subject who has an abnormally high heart rate exhibited high exponents (as high as 1.4). A Human transplanted heart, which has no nervous controls, exhibited exponent 1.2. The fluctuation of the heartbeat interval contains information for the risk of a cardiac cessation or mortality.

Keywords: Heart, EKG, Brain Control, DFA, Model animal, Crustaceans.

1. INTRODUCTION

The heart is a restless organ system. Not only in vertebrate animals but also in invertebrates, they have the heart system, a pump and a controlling brain center. Modern molecular biology revealed that the biological development of the heart system is governed by common genes [1]. A basic mechanism now seems to be identical for all 'hearted' animals. Experiments on human hearts are practically impossible. Crustaceans are thus a good model of specimens for the research on neurodynamical control of the heart. We here show the results of DFA of various heartbeat-interval data and propose that DFA can be a tool to describe the risk of cardiac cessation or mortality.

2. METHODS AND PROCEDURES

We have described the crustacean cardiovascular control mechanism elsewhere [2]. Our DFA-computation method has already been explained elsewhere [3].

We recorded the EKG from freely moving animals using permanently implanted metal electrodes. Signals were digitized mostly at 1 KHz, stored, and processed by a Power Lab (ADI, Australia). Human heartbeats were recorded from the finger's blood pressure change, using a Power Lab.

In the present study, we used *Crustacea*; two large-sized, air-breathing, tropical crab species, the coconut

crab, *Birgus latro* ($n = 3$), and the Mokuzu crab, *Eriocheir japonicus* ($n = 3$). Heartbeats were observed chronically with a long recording. The crabs were maintained at room temperature, at ~20 degree Celsius but it varied with the natural weather. Anatomy and physiology of the crustacean hearts have well been documented before [4-6].

Scaling exponents

Our previous experiments revealed that the lobster heart without a brain-control exhibits a scaling exponent of 0.5. But, the scaling exponents approach to 1.0 if the heart is intact [7].

Does the scaling exponent change when animals are sick? Can DFA predict a forthcoming life-threatening disaster, like the cessation of the heartbeat? Can it uncover "hidden information" regarding to health? Those are physiologically attractive questions, as Goldberger and his group [8] indeed pointed out. Experiments on human hearts are inadequate. We used a model animal, the crustaceans.

A model animal and its benefit

A large-sized crustacean has a low risk against the potential damage of the heart tissue from an implantation of EKG-electrodes, and the high advantage for obtaining larger EKG signals, which allow us to easier measurements of the beat intervals, due to a better signal noise ratio.

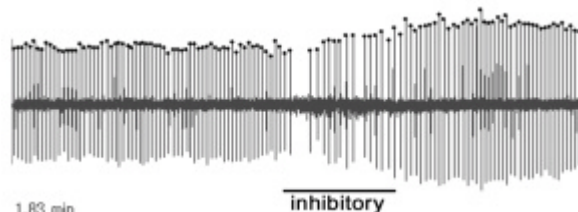


Figure 1. EKG of a healthy coconut crab, which is arecord for the period of 1.83 min. It is known that healthy crustacean hearts intermittently make a slow down in rate. The cardio-inhibitory nerves contribute to this rate-change (see a bar). Typically a post-inhibitory rebound excitation is seen in the diagram.

At first we needed healthy models. A tropical crab was captured on Okinawa (latitude 24 degree North) in March of 2004 and was cultured until September in Ebina near Tokyo

(latitude 35.5 degree North) with continuous EKG sampling. The crabs originally live in southern Japan and were moved to the north, where they were maintained well, until their life came to an end.

EKG peaks were identified by a PC program but all peaks were confirmed by eyes on a beat-to-beat base (see dots on each spike in Fig. 1). Our own program calculated intervals of beats and computed the scaling exponents (see the ref [3]).

3. RESULTS

A healthy coconut crab

The scaling exponents varied. On Mar 18, the first day, the scaling exponent was 0.83. On March 26, two weeks after the capture, it showed 0.99, during a nocturnal active period. During the stressful morning period the scaling exponent was 0.83. On this morning, humans approached the container for changing water and cleaning the container. During the daytime on March 26, a sleeping period for the nocturnal animal, the exponent increased to 1.2. The crab lived in a healthy condition for more than half a year. The scaling exponents showed 1.0 on Apr 7. The healthy conditions lasted until Aug 30, with an exponent of 1.0.

In a human heart, 1/f type fluctuation (scaling exponent 1.0) has been demonstrated [8]. "Hearted" animals on the Earth might exhibit 1/f type noise in heartbeat fluctuations, if the subjects are healthy. Healthy hearts in animal models and humans, behave in quite a similar manner. This is the consequence of evolution and genetics [1].

Naturally dying coconut crab

Dying is the most catastrophic condition in life. We expected that therefore exponents changed dramatically at this state. This is the reason why we focused on the "terminal conditions."

After a hot humid summer season was over, in mid September, the climate changed to colder weather. The crab got sick, and become less active even at nighttime and exhibited less appetite. On the 4th of October the EKG changed for the worst and finally the crab died. Figure 2 shows EKG over 18 hr when the life came to an end. At the period *A* 18-14 hr before death, the exponent was 0.86. Although the amplitude of the EKG changed violently, the exponents remained rather steadily for 13 hr (see from *A* to *D*).

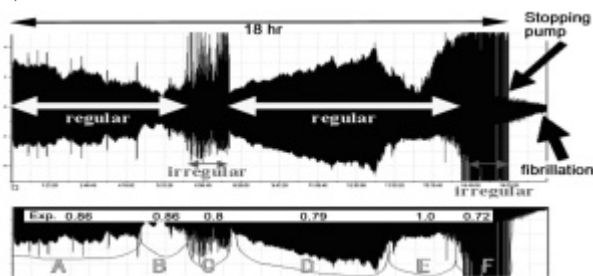


Figure 2. Coconut crab. EKG and DFA on the last day when the crab died. After stopping to pump, there remained fibrillations. The amplitude of EKG signals varied significantly, we divided 18 hr into 6 different periods, from *A* to *F*, as indicated in the figure. Scaling exponents corresponding to each period were calculated as shown in the insertion. *A*, *B*, *D*, and *E* are relatively regularly beating periods. However *C* and *F* are irregularly beating periods. Regularity/irregularity did not always correspond to scaling exponents. Period length; *A*, 00:00-04:00, *B*, 04:00-06:00, *C*, 06:00-08:00, *D*, 08:00-13:30, *E*, 13:30-16:00, *F*, 16:00-18:00.

During the sick period, we saw less active locomotion, no intake of food, and an exponent of 0.8-0.86. Interestingly, the scaling exponent increased during the period *E*. We designated it as: "recovered stage of 1.0". Then the exponent

finally dropped to 0.72, and the irreversible stopping beat of the heart occurred.

Figure 3 shows part of the EKG and heart rate for the corresponding period (*A* to *F*, see Fig. 2) in an expanded time scale. A change in amplitude, decrease in heart rate, and a not-always-identical pattern of fluctuation can be seen.

Figure 4 shows examples of individual muscle potentials for corresponding periods (*A*, *B*, *D*, *E*, and *F*) with exponents displayed.

The scaling exponents do not correspond well with the amplitude of spikes, the shape of action potentials, and the rate of beatings. It seems that a detailed inspection of an EKG cannot evaluate "hidden information" about a cardio-vascular dysfunction-related mortality. Fluctuation could carry "hidden information". We might possibly uncover the risk of death from DFA (exponents in Figure 2) but not from a general EKG and heart rate (Figure 3 and 4). We already reported that a frequency analysis (general Fourier analysis) of the EKG was also not satisfactory in the lobster [12]. We concluded that the intense decline of exponents is an indicator for the cardiac arrest in the near future.

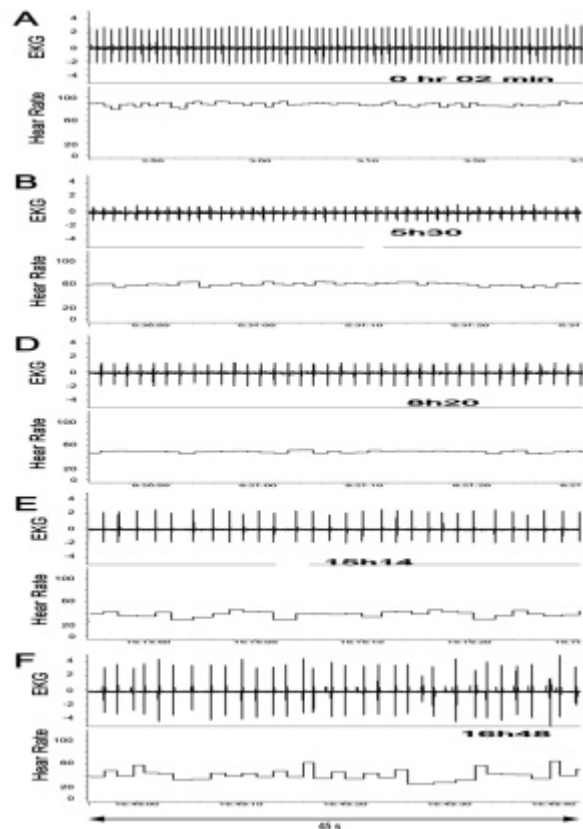


Figure 3. Coconut crab. Part of the heartbeat record in an expanded time scale. EKG for 45 s and heart rate is shown. The same heart shown in Fig. 2.

Terminal condition with natural death

During the period *E*, the exponent has recovered. It was elevated up to as high as 1.0 (see Figs. 2, 3 and 4). What does this mean? Was it an indication for the forthcoming disaster, the cardiac arrest? This question was confirmed in the next several experiments performed on the large sized crabs (see Fig. 5). We discovered that four different crab species, which had "died naturally" all exhibited a "recovered stage of 1.0" (not shown). We propose that a "recovered stage of 1.0" in DFA is useful for a terminal diagnosis. Once the heart exhibited the "recovered stage 1.0", during a terminal decaying process in a natural death, the irreversible cessation of the heartbeat is almost approaching.

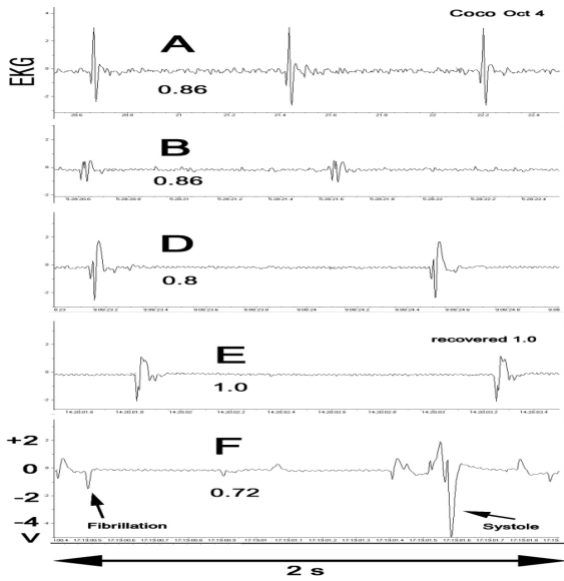


Figure 4. Coconut crab. Individual myocardial spikes in the EKG and scaling exponents. The same heart shown in Fig. 2.

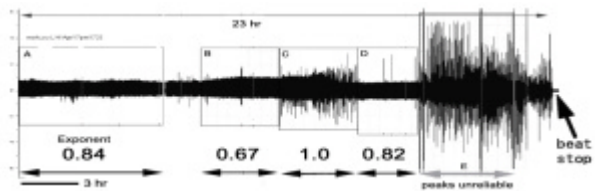


Figure 5. Another example for the natural death. A big Mokuzu crab EKG for 23 hr. This healthy crab was captured on Ogasawara Island, Japan. The experiments were performed in Ebina as with the coconut crab. Scaling exponents were calculated independently at the corresponding periods, A, B, C, and D. But, in period E, we gave up the computation since the recording is too noisy.

Heart injury death

A natural death was characterized by a decrease of exponents. However, we noticed that crabs, which died after a failed surgery because of the difficult electrode implantation, exhibited a surprisingly high scaling exponent (Figs. 6 and 7). The high exponent was maintained from the beginning of the experiment (not shown) until the very end of its life. Diagnostically, it was hard to tell/predict the very last moment (sooner or later) from the scaling exponent, since the exponents were always high (Fig. 7). Heart cessation happened relatively suddenly. The injured heart did not exhibit fibrillation after the cessation (Fig. 6).

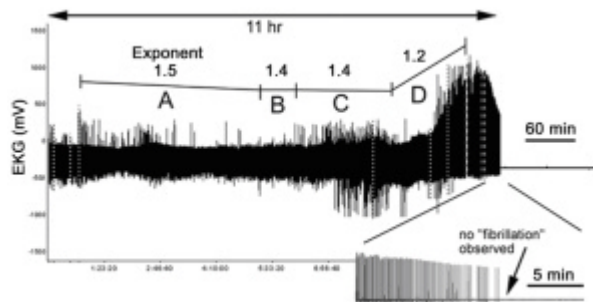


Figure 6. Heart injured crab, a big Mokuzu crab, *Eriocheir japonicus*. EKG during the last 11 h of its life. The inset shows the last moment in an expanded time. The scaling exponents are presented in corresponding zone, A, B, C and D.

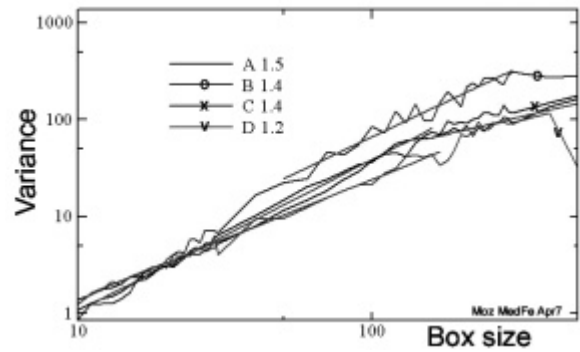


Figure 7. DFA computation on heart-injured model shown in Figure 6. The inset shows scaling exponents, that express a slope of each fit. The periods A to D correspond to those shown in Figure 6.

Myocardium dysfunction model

Two Mokuzu-crab's results are shown in this report: one is in Figure 5 and the other one is in Figures 6 and 7. The two are identical crab species, captured at the same time on the same island, and their EKG experiments were performed in parallel, i.e., by a multi channel EKG recording in the same room but in a different container. Most importantly, the two died from different reasons.

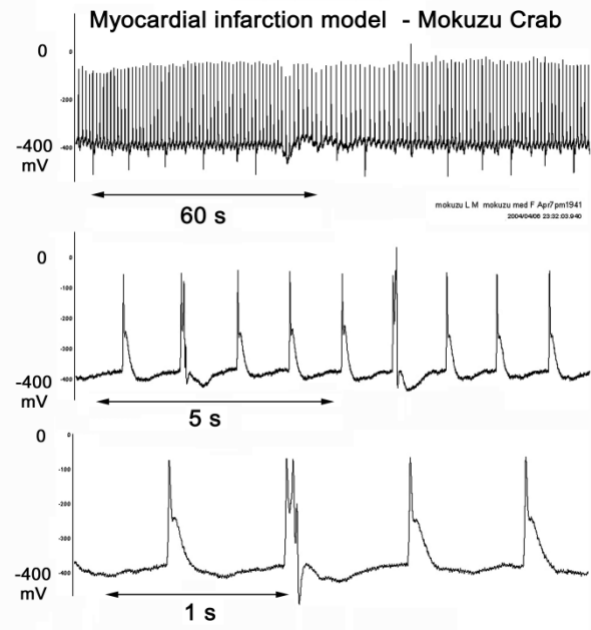


Figure 8. EKG from a Mokuzu crab which died due to a myocardial injury. Three traces are shown in a different time scale, to show the configuration of abnormal potentials. It can be seen in the traces that abnormal beats are generated every several beats. The same crab with Figures 6 and 7.

The Mokuzu crab normally lives in a river. But, we captured them on land, because they are on land only during the mating season. Therefore, they also can survive outside of the water, in the air. No deep-water flow was supplied because of the acceleration of death, for the beneficial quicker experimentation. The crab in Figure 5 died naturally. It survived for 20 days. The crab in Figures 6 and 7 died due to a mechanically wounded heart. It survived for one week. The damage was so serious to distort the EKG potentials as indicated on EKG traces (Fig 8).

Figure 8 shows that abnormal spike potentials are generated once every several beats. Electro-physiologically speaking, the abnormal spikes have double spikes, which are

caused by undesirable depolarization of myocardial cells. The depolarization is caused by a cell-membrane-damage with metal electrodes. Such a mistake is inevitable sometimes. But the outcome of these experiments gave us a data from both, a natural death and an injury death.

It is known that a normal crab heart intermittently takes a rest (see Fig. 1), which is executed by inhibitory nerves from the cardiac center in the brain [6]. In crustacean animals which hearts were injured or which received stress from the environment, the intermittency is lost [11]. We thereby easily can recognize the sick symptom by identifying a continuous regular beating [11], instead of a repetitive slow down that is normally observable in healthy crustaceans [9]. Experiments on injured hearts revealed that an injured heart exhibits a high scaling exponent. In such subjects, we confirmed that the heart rate is elevated.

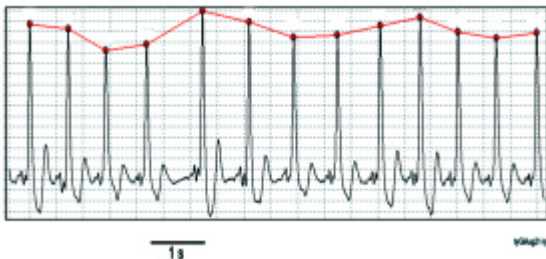


Figure 9. Fluctuation patterns in a human subject. This subject rarely but certainly has this symptom of arrhythmia (note a 1 s bar; interval of underlined part is elongated). Heartbeats were recorded from finger blood pressure in a seated position.

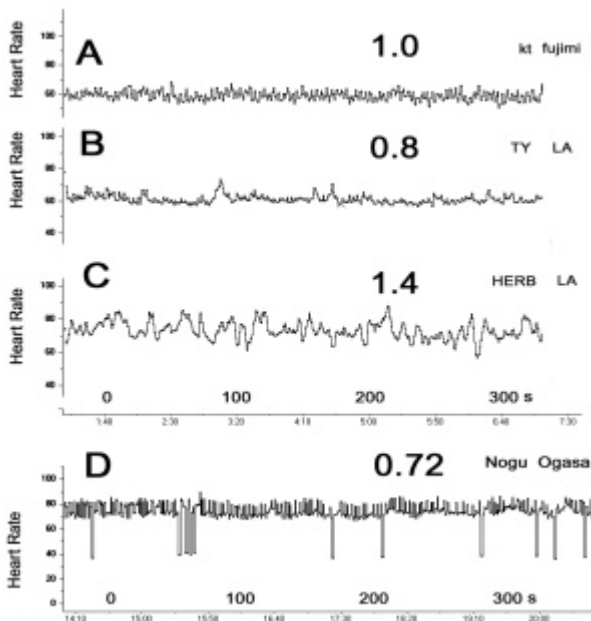


Figure 10. Fluctuation patterns and scaling exponents in humans. All heartbeats were recorded from finger blood pressure in a seated position with a relaxing talk for 30 to 60 min. *A*, normal, healthy subject, exponent 1.0. *B*, apparently normal subject but rarely exhibits arrhythmia symptom (not detected here), exponent 0.8. *C*, a tall big man, his heart rate is much higher than expected from the size of the body, with an extremely high exponent 1.4. *D*, subject who has frequent arrhythmia, exponent 0.72. Subject *D* is a very small man, thus a high mean heart rate ~ 80 is normal. In turn, subject *C* is a big and tall man (not fat), thus his mean heart rate ~ 75 is too high. It should be much lower than typical size man like in *A* and *B* (B is little smaller than *A*) at such a relaxing seated condition.

DFA on human subjects

We tried to observe the heartbeat of various humans in different countries. Figure 10 shows a fluctuation pattern and

scaling exponents of four subjects. DFA revealed that normal healthy subjects had an exponent near 1.0 (Fig. 10A). Those healthy subjects showed no abrupt elongation or shortening of heartbeat intervals. The fluctuation looks like “random” by eyes. We have obtained so far such healthy data from about 20 subjects who as exponent of ~ 1.0 .

A subject who rarely but certainly has a symptom of arrhythmia (Fig. 9) showed an exponent of ~ 0.8 (Fig. 10B). The data shown in Fig. 9 and Fig. 10B are obtained from identical subject but different occasion of recording. Abrupt elongation of interval shown in Figure 9 is representative but rarely occurring arrhythmia, thus yearly health-check only detect it once in his life. But, DFA analysis detects this rare incidence, by a low exponent, and makes a warning that the subject’s control system might have problem, as a 5, 10, or 20 years long time scale forecast. We have three such example subjects. We have never observed any abnormality (just like Fig. 9) in healthy subject who has exponent of ~ 1.0 (just like Fig. 10A).

A subject who has frequent arrhythmia showed an exponent of ~ 0.7 (Fig. 10D). We have three such examples. An abnormal subject has an exponent of 1.4 (Fig. 10C). This man has two brothers. Both of them had already died with cardio-vascular problem.

Human transplant heart

We have a case study on the transplanted heart [10]. Several months have past since the operation. No re-innervations have established at this stage. Therefore, heart controls are, if any, executed by a hormonal way. High heart rates and high exponents, 1.2, were observed (Fig. 11). (courtesy of Vaughan MACEFIELD, Prince of Wales Medical Research Institute, Sydney, NAW 2031 Australia)

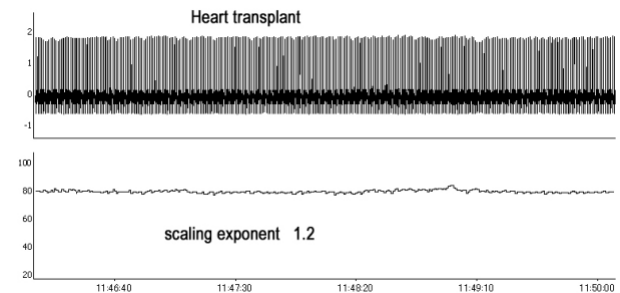


Figure 11. EKG, pattern of fluctuation and scaling exponents in transplanted human hearts. DFA computed exponent 1.2. Heart rate is relatively high and very steady fluctuation.

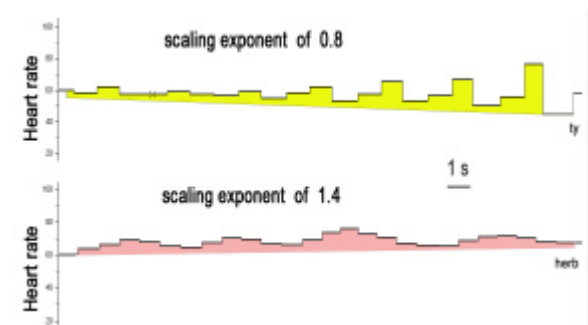


Figure 12. Unusual pattern of fluctuation found in subjects who has abnormal exponents. Upper subject: the same person of Figure 10B. Three-beat regularity can be seen. Lower subject: the same person of Figure 10C. A slow regular oscillation can be seen. Both rhythms are apparently not “random” and therefore not normal. The normal subject of Figure 10A (exponent ~ 1.0) never shows patterns like this.

Abnormal exponents is a warning light

The subject shown in Figure 10 B and Figure 10 C looks healthy. But, the DFA of them have made a caution: *B*-subject has a low exponent (0.8) and *C*-subject has a high exponent

(1.4). We therefore inspected detail of their fluctuation patterns (Fig. 12).

Figure 12 indeed demonstrates that unusual fluctuations are detectable in the cardiac-pulse-record of subjects who have diagnosed as a person who has unusual scaling exponents, such as 0.8 and 1.4. As shown in Figure 12, too much regular patterns are seen in those records. Unfortunately, in terms of mathematics or physics, as well as in physiology, we so far do not understand the mechanism or causality for leading to a change of the exponent. However, we at least understood that when there is a wrong exponent wrong beatings are hiding in the record and the subject denotes unhappy feeling. Two examples are shown below.

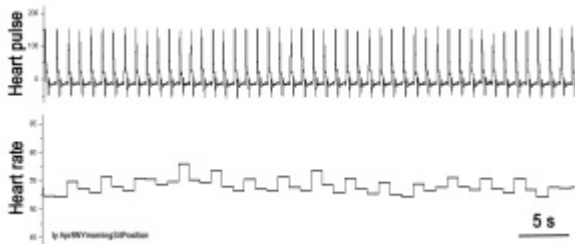


Figure 13. Unusual pattern of fluctuation found in subjects who has abnormal exponent of 0.8. Extraordinary periodicity can be seen. It is apparently unusual but potential risks for the cardio-vascular failure are so far not identified. The same subject of Figure 10B.

Since the subject of Figure 11B has got a low exponent of 0.8, we inspected his pulses repetitively. And, we detected unusual patterns in his pulse record, such like Figure 13. Figure 13 shows a ill-feeling example although more study is necessary. This subject feels indeed unhappy. This type of pattern is never seen in normal person, like that in Figure 11A.

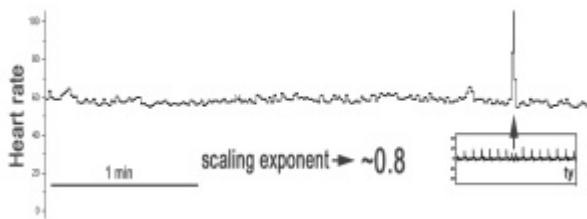


Figure 14. Unusual pattern of fluctuation found in subjects who has abnormal exponent. A brief but extraordinary high rate of beating can be seen (inset shows a pulse record). It is apparently unusual. A potential risk for the dangerous tachycardia for this subject might be pointed out by the scaling exponent of ~ 0.8 .

Figure 14 is another an unhappy-feeling example for the subject of Figure 10B. We detected unusual but rarely-occurring tachycardia-like dangerous patterns in his pulse record, such like Figure 14. In this case, the subject had very unhappy feeling. The small successive ventricular two contractions at a high rate may have risks leading it to so-called tachycardia, the sudden death, but we hardly tell “when” from this record. At least, this type of pattern is never seen in normal person, like that in Figure 11A, who has a scaling exponent 1.0.

4. DISCUSSION

The present analysis on a dying crab revealed that the scaling exponent reflects a change of the control system. A study on *Crustacea* models is unique and new. The results on the models is applicable to the human heart. For establishing tight connection between scaling exponent and body condition (both heart condition and controller condition), further experiments are necessary. However, we can point out useful technological perspectives from a physiological point of view.

Natural death

Naturally dying crabs showed a gradual decrease of exponents (Figs. 2, 3, 4, and 5). From these examples, we propose a hypothesis: if we are in a serious condition, and if we know the normal exponent value of ourselves, we might be able to estimate the risk of mortality by determining the degree of the decrease of the exponent. However, this working hypothesis is to be elucidated more precisely. The decrease of the exponent must be caused by the spread of a complex cell-biological dysfunction throughout the body, not by a single deficiency, such as vitamin deficiency, for example.

The followings are scenarios in physiology. Complex changes occur in a naturally dying body. The metabolism is deteriorating and thereby a fluid composition is forced to change. The potassium concentration increases significantly. It causes depolarization of a variety of cells including neurons and heart muscle cells. If the body is healthy, at rest, most of the animal cells keep deep resting membrane potentials (meaning: in higher minus values, like -70 mV). This healthy state allows most of the cells to stay inactive and allows a resting state. Neurons and muscle cells keep silent at a resting state. If the deterioration begins, extra-cellular potassium concentrations increase. Resulting in a membrane-potential-decrease (meaning: lower minus values such as -40 mV, i.e., depolarization) triggers Ca^{++} release from the internal Ca^{++} store (for example, endoplasmic reticulum of muscle cells). This trigger-action is not regulated biologically. Many chemical reactions start arbitrarily. For example, the pancreatic/renal/liver cells release hormones to the circulation without necessity, caused by unexpected increase of Ca^{++} intracellular concentration in those many cells. Waste chemicals and litter molecules are not efficiently removed from the circulation, because the renal/liver cells cannot work efficiently due to a cellular dysfunction, causing an ionic imbalance of body fluid. Potassium ions, which are normally captured in an intracellular space, leak out. Increased extracellular potassium ions enhance the cell depolarization further, thus a deterioration of cells takes place more likely. The body is caught in a vicious circle. Finally, cardio-regulatory nerves discharge impulses very actively, due to the uncontrolled depolarization. This state is complex but probably looks like very active and apparently less problematic thus pseudo-healthy conditions can be established for a while. This pseudo-healthy condition makes the scaling exponent going back to normal, the “recovered 1.0” although further investigation is necessary.

Cardiac death

Injured heart showed a high exponent and a high mean heart rate. Mean heart rate was elevated because an inhibition was totally removed. It is obvious that the control system has changed by the heart injury. However, the muscle potential kept normal configurations throughout their life (not shown). This indicates that the activation-inactivation process of ionic channels (sodium channel and potassium channel are most important) are sequentially well organized. This proves that an ionic composition of fluid in which ionic channels are soaked is not significantly altered by a heart injury. It is certain that the body system must have worked properly until immediately before death occurred. In other words, being in good shape with muscle potentials, is the evidence that internal fluid is well maintained until the end of life.

Why does the scaling exponent go up over 1.0? A tentative solution is that the control system has changed, and thereby the exponent was elevated. A sick heart in a healthy body elevated the scaling exponent over 1.0. We do not have good physical and mathematical interpretations yet.

However, we have a physiological scenario as follows. Heart muscle cells are only partially damaged by electrodes. Only the heart has a small problem due to a partly failed surgery. The heart is only partially damaged but it can be compensated through acceleration of the heartbeat. Acceleration can be accomplished in two ways. One is the nervous excitation of the heart. The other one are the acceleratory hormones, such as biogenic monoamines. We have proved a significant increase in concentration of stress-induced amine [11]. If the heart becomes weak and

propels less blood due to electrode damage, the feedback command sets up the acceleration. The damaged heart showed no intermissions of heart beats (for intermission, see Fig. 1). A damaged heart has therefore not the time to take a rest in pumping, which a healthy crab always does at rest. In the present study, the sick crab lost the intermittent cardiac slow down. Its heart worked hard and finally it stopped beating. High exponents like 1.2 to 1.4 is a dangerous sign. Although it is hard to tell when the sudden death will come, high exponents might be the caution for the risk of a sudden cessation, at least in animal models. It is reported that 43 % of the human heart attacks are undiagnosed (British Cardiac Society News, 20 February 2006). We do not know whether the 43 % subjects had a high scaling exponent. But the present animal model is an intriguing example for the risk forecast in terms of computation technology.

Medical application and computation technology

Injured hearts in the present study gives a model for human cardiac disease, such as long QT syndrome, which is caused by a genetic mutation of sodium and/or potassium channels. The mutation changes protein structures of myocardial ionic channels. The mutation causes abnormal ionic flow resulting in an abnormal shape of myocardial potentials. Especially the mutation causes elongation of the period of depolarization [12]. The abnormality induces unexpected elongation of a depolarization-period and therefore induces a high frequency discharge of muscle potential, because of a longer maintenance of depolarization, which could induce extra spike potentials that is observable in animal models (see Fig. 8). If the extra spikes occurred repetitively, this is a life-threatening tachycardia that is known to happen in humans.

We have not yet tested the diseased human heart. The long QT may or may not affect DFA results. According to our present model experiments, dysfunction of the heart has at least caused abnormality of the control systems. The control system impairment could be detectable by DFA.

Our hypothesis is as follows. Once the heart has reached this state of this problem, such as infarction, partial myocardial damage, the control center tries to modify the cardiac regulatory pattern. Because, the center needs to compensate the decreased cardiac output per each contraction. For example, a decreased cardiac output triggers an enhanced rate of contraction by a feedback mechanism. This compensation could be accomplished in both, neuronal and hormonal ways. We observed this type of compensation in the present study. High scaling exponents were observed in three examples. (1) Injured heart of crab animal models (Figs. 6, 7, and 8). (2) Abnormal human subject at a high heart rate, who probably has family-linked genetic problem but uncertain (Fig. 9C). (3) Heart transplant subject (Fig. 10). We propose that central compensation for the cardiac control method, details that are unknown, affect DFA exponents. The changes in the complex system of cardio-vascular controller necessarily occur when the heart itself has problems of being induced by either mechanically or genetically defects. In such case, we will have a high exponent. If this hypothesis is proven, our computation method could be accepted widely.

5. ACKNOWLEDGEMENTS

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