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Alternans generation in the crustacean heart model: a simulation - electrophysiology study

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Abstract– Alternans-rhythm indicates an unhealthy state of the heart but this 2-beat rhythm is still required for further studies since the ionic mechanisms are not fully understood. With gathering real-world data of alternans, we characterize its ill-condition using modified detrended fluctuation analysis (mDFA) and we also argue ionic mechanisms for generating alternans based on a numerical simulation. Alternans-electrocardiograms were recorded from various "hearted" animals including humans. We found: (1) Alternans decreases the scaling exponents, which can quantify the state of the circulatory system. (2) Simulation analysis reveals that mainly K+ and/or Na+ ionic mechanisms can explain how and why the heart system generate alternans.

1. Introduction

The cardio-vascular system (CV) is a most incredible organ system in our body. It never stops to repair itself [1]. The CV is composed of a pump and a controller, i.e., the heart and the brain, respectively. The hearts are able to pump even after the isolation from the CV. Therefore, we understand that the heart has an automaticity, i.e., it has its own pace-maker. The pacing mechanism is completely intrinsic, generating electrochemical signals to keep a non-stopping blood flow throughout the body until the end of its life. However, the rhythm of the electric signals are never constant and regular, because the brain changes the rhythms according to local body's demands, such as oxygen necessity to work out various body cell functions, locomotion and digestion for example.

When the heart beats, the intrinsic oscillator produces a signal which is a mixed/complex flow of ionic currents, flowing through the ionic channels locating in every cell membrane of the heart muscles. The pace-making is an incredible bio-chemical and bio-physical outcome generated from the complex cellular ions-proteins-water system. Due to its complexity, it is hard to identify the causes of circulatory failure, if the complex system gets a malfunction. The complex cellular ions-proteins-water system receives influences from various functional elements, which are coupled nonlinearly together, for instance, an electrical coupling between myocardial-cells, hormonal influences derived from the brain, and cardio-regulatory neuronal commands from the brain, as well as a reflexive feedback control, between the heart and the brain. Since an electrocardiogram (EKG) was made by Willem Einthoven (the Nobel Prize in Medicine in 1924), a century have passed. But there are still so many people suffering from the cardio-vascular disease. We still need to make an effort to find out solutions to stop the life threatening disease. Our ultimate purpose throughout this study is to protect/stop the system from malfunction.

2. Alternans

One of the fatal rhythm is "the harbinger of death rhythm [2]," so called as alternans, which was documented in 1872 by a German physician Dr. Traube [3]. This 2-beat rhythm is, therefore, a well-known fatal disturbances (perturbation) in heart rhythms. However, the mechanisms for this erratic rhythm generation has not been fully understood.

Two-beat rhythm might be a sign of unhealthy state of the pumping of the heart. When does this unusual rhythm happen to us? We still do not know the reason why it is generated. In fact, Traube [3] noticed this enigmatic rhythm in human patients long ago. However, we found that it is not confined to human hearts. Here we report that alternans-like heartbeats are observable everywhere in "hearted" animals. Animals are all the same. Alternans is a fundamental phenomenon for the life on Earth. We found examples for the 2-beat EKGs recorded from various creatures, such as insects and crustaceans, as well as from human subjects. Furthermore, using mathematical simulation methods [4], we present compelling evidence for that the generation of alternans depends on the blood-concentration of potassium ions and/or the degree of membrane conductance of sodium ions. We discuss ionic bases for explaining abnormality related to interactions between potassium and sodium ionic-flow of the heart muscles.

3. Materials and Methods

3.1. Electrophysiology

Electrophysiological recording methods are described elsewhere [5]. Using our electrophysiological methods, we gathered real-world data, EKGs (Figure 1).

Heart rhythm never keeps a constant frequency. As aforementioned there is a necessity of changing the rhythms for meeting demand of the body. In healthy individuals, the heart rate is changeable under the control of the brain. Disturbances of regulation of healthy heart rhythms are thus sometimes extremely fatal, where the heart can beat erratically.

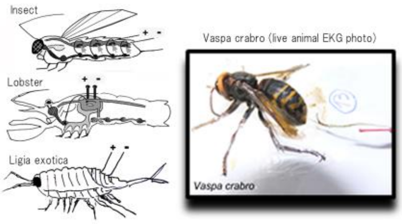

Figure 1: EKG recordings from invertebrate animals.

3.2. Simulation

Simulation methods are described elsewhere [4]. We studied ionic currents with the numerical simulation that can see healthy/unhealthy state by changing parameter(s) in a set of numerical models.

3.3. Ethic

The heartbeats were recorded outside of a hospital, in for example university laboratories. All subjects were treated as per the ethical control regulations of Tokyo Metropolitan University.

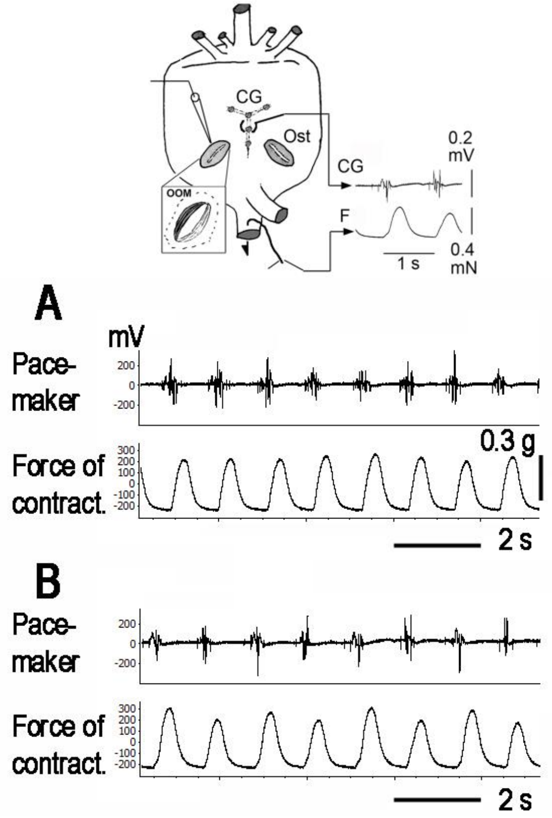

Figure 2: Regular (A) and irregular (B) heartbeats. Inset: a diagrammatic drawing of an isolated crustacean heart, simultaneous recording of pacemaker impulses (CG) and contraction force (F).Hermit crabs, *Dardanus crassimanus*.

4. Results

4.1. Crustacean isolated heart

Isolation of the heart from the body (Figure 2A) easily lead the heartbeat into arrhythmic condition (Figure 2B). Isolated hearts must die sooner or later. This is evidence that alternas is the harbinger of death rhythm, although the mechanisms remains to be elucidated.

4.2. Crustacean intact heart

Long term EKG recordings from various invertebrate animals (see Figure 1) revealed that alternans always appears before the animals die (Figure 3).

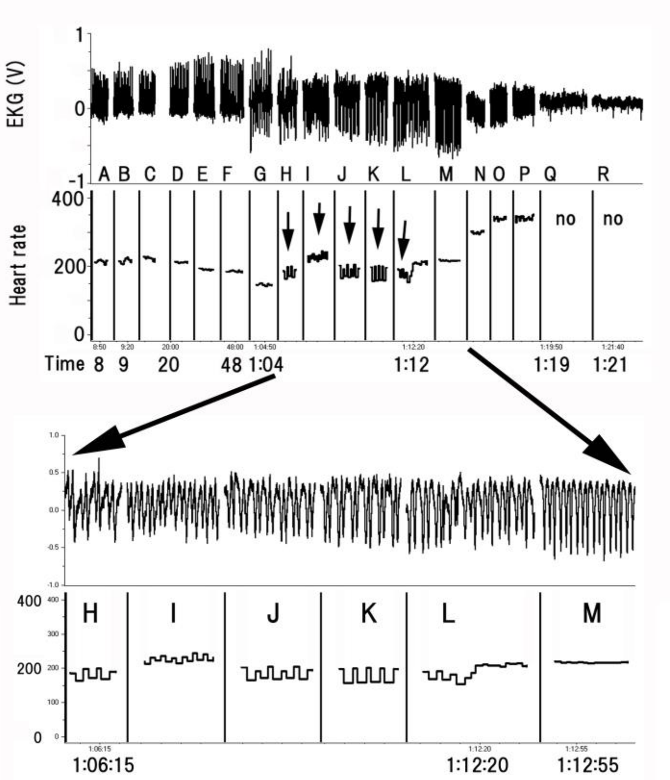

Figure. 3: EKG and heart rate of a dying crustacean, isopods, *Ligia exotica*. Two metal electrodes, 200 micrometer in diameter, were placed on the heart by penetrating them through the dorsal carapace (Figure 1). A sticky tape on a cardboard immobilized the animal. Records are shown intermittently for 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. (After T. Yazawa et al., reference [6])

4.3. mDFA: crustacean heart alternans

Modified detrended fluctuation analysis (mDFA) was recently made [7], which can quantify either a healthy heart or a sick heart, such as ischemic failing hearts. We used mDFA method to calculate the scaling exponent (SI, scaling index) using “the heartbeat time series analysis.” mDFA can tell that a healthy heart exhibits an SI near 1.0 but a sick heart, such as dying heart exhibits a lower SI, ~0.7 for example (see detail reference [7]).

Figure 4 shows examples of the heartbeat interval time series, obtained from EKGs of a spiny lobster, one is isolated (Figure 4A) and the other one is an intact heart (Figure 4B). mDFA computation revealed that isolated hearts exhibit an SI ~0.6 and intact hearts exhibits SI ~1.0 (data not shown).

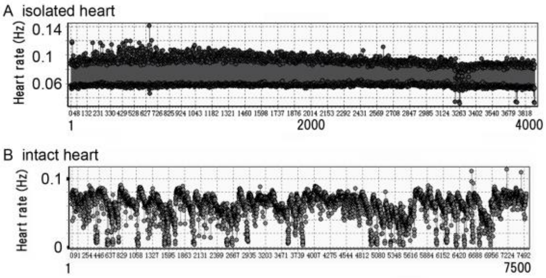

Fig. 4: Heartbeat interval time series obtained from an isolated (*A*) and intact hearts (*B*) of a spiny lobster, *Panulirus japonicus*. *A,* Alternans appeared all the way down from the first beat to the 4000th beat. *B,* An intact heart of a spiny lobster, *Panulirus japoniculs*. No alternans appeared. The heart rate (shown in Hz) frequently dropped down, so-called bradycardia, which is known in normal crabs and lobsters [7]. The present mDFA revealed that the scaling exponent is normal (1.0) when the lobster is freely moving in the tank [7]. (After T. Yazawa et al., reference [6]).

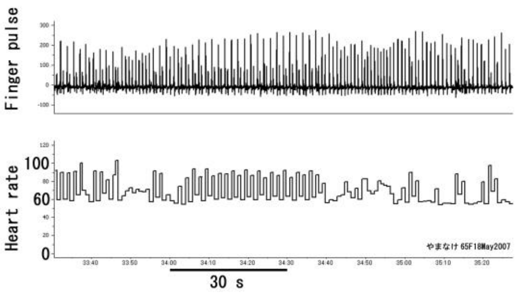

Fig. 5: Alternans observable in human. A volunteer woman age 65. Upper trace, recording of finger pulses. Lower trace, heart rate. Both amplitudes alternans and intervals alternans can be seen. (After T. Yazawa et al., reference [6]).

4.4. mDFA: human heart alternans

In human, alterns also shows a low SI (Figure 5). Her SI was near 0.6. She passed away two years after this recordings. She suffered from cancer and pancreas problems. When we met her, she was physically weak and she could not 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.

4.5. mDFA results: overview

Alternans heartbeats always decrease SI value. Figures 6, 7, and 8 show representative three “alternans hearts,” including two human hearts and one lobster isolated heart. Figure 6 shows mDFA results where all three time series exhibit a low SI while many alternans heartbeats appeared. Figures 7 and 8 show enlargements of corresponding time series in an expanded time scale (note bar periods and beat number).

4.6. Simulation

An alternans simulation study conducted by H. Kitajima has appeared elsewhere [4], where he revealed that alternans generation is caused by a shift of potassium ion concentration in blood and membrane permeability of sodium ions over the myocardium.

His conclusion was wonderfully simple, which is shown as a diagram in Figure 9. Here, one can see a parabolic relationship between potassium-ion and sodium-ion function determining the myocardial cell membrane excitability. The point A in the graph shows the state of “normal,” where both “sodium permeability” and “extracellular potassium concentration” are “normal,” i.e., a healthy range of the excitability.

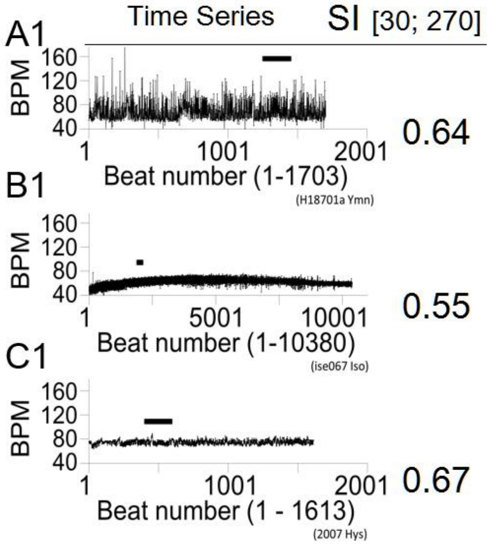

Figure 6: Alternans real world data. Four example time series. A, human subject shown in Figure 5. B, lobster specimen, isolated heart shown in Figure 4A. C, human subject, male, age in his 60s.

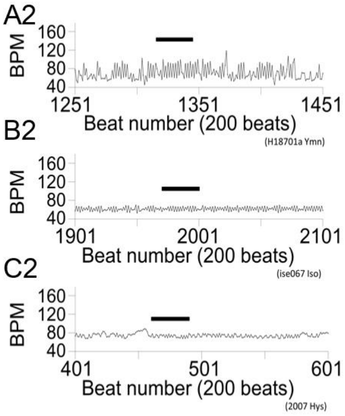

Figure 7: Time scale expanding. See the period shown by a bar in Figure 6: see also beat numbers in x-axis.

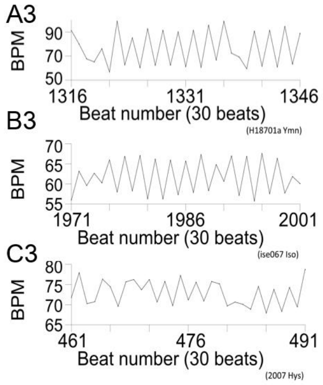

Figure 8: Time scale expanding from the period shown by a bar in Figure 7.

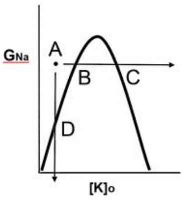

Figure 9: Simulation results of alternans-generation (modified after ref [4]). G_{Na}, sodium permeability, $[K]_o$, extracellular potassium.

5. Discussion

Alternans is a sick state of the heart [2, 3]. Alternans generation was never reported before in invertebrate hearts. We found alternans in many specimens, which include crabs, lobsters, insects, and humans. Typically, all of them were found while specimens were dying (Figure 3). We conclude that the harbinger of death rhythm is observable not only in human hearts (Traube's first documentation) but also in many "hearted" lower animals. The present study proves that, evolutionally, alternans is arising from the basic physiology mechanism, which is common to all "hearted" animals.

The mechanism is well characterized by Kitajima's simulation [4], which explains ionic mechanism for the generation of alternans. What are the causes? It is a membrane potential shift towards a depolarizing direction (see Figure 9). An increase of blood K+ (a shift from A to B, and B to C) depolarizes the membrane according to Nernst (see Physiology text book). At B, here, a regular rhythm drastically changes to 2-beats rhythm. This correspond with a natural data (see Figure 3). From B to C, further depolarization maintains alternans state (see also Figure 3). Further depolarization returns the heart to a rhythmic state (Figure 9). But this is an extreme state, not normal. At this point, the heart enters sick and terminal state as shown in natural data (Figure 3) where the heart rate increase significantly and animals are dying.

Blood sodium concentration is high (~40 times) compared to that of potassium. Significant decrease of blood sodium ions is not realistic to happen. But if sodium permeability decreases, alternans can happen. (Figure 9, from A to D). This explains a genetically induced Na+ channel problem. The simulation worked well to understand causes of alternans, together with natural data.

Alternans is a risky state for maintaining life. mDFA can quantify this state (Figures 4, 5, and 6). Decreased SI indicates a sick state where a heart endures a condition of unhealthy (failing) heartbeats. Main causes for alternans are therefore K+ induced deadly and irreversible depolarization of heart muscles. This state is hyper K+ in blood.

Acknowledgments

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