—Review—

Sudden Cardiac Death from the Perspective of Nonlinear Dynamics

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There are some reports that sympathetic nerve activity (SNA) shows a characteristic pattern a few hours before the onset of lethal ventricular arrhythmias. If so, it could be possible to predict sudden cardiac death a few hours in advance of its occurrence. Recently, we reported that a previously unidentified V-trough of SNA is a potential precursor of lethal cardiac events by examining 24-hour ambulatory electrocardiograms in which such an event was recorded by chance. In contrast, the chaotic nature of heart rate variability has been noted recently from the viewpoint of nonlinear dynamics. This study models the hemodynamics, consisting of heart rate, SNA, and blood pressure (BP), by modifying a known chaotic electrical circuit, the Chua circuit. A V-trough of the SNA appears when the resistive element between the SNA and BP in the circuit is increased, which corresponds to the impaired regulation of BP by the SNA. This finding is consistent with an acknowledged finding that a depressed baroreflex (a reflex of the BP by SNA) may trigger a lethal arrhythmia. This study indicates that a V-trough of the SNA is a possible precursor of sudden cardiac death on the basis of experimental and clinical findings as well as mathematical modeling. (J Nippon Med Sch 2018; 85: 11–17)

Key words: sudden cardiac death, ventricular fibrillation, autonomic stress, chaos

Structure of this Review

The section on the epidemiology of sudden cardiac death (SCD) describes how the increasing number of SCD victims is a social problem. Next, excessive sympathetic nerve activity (SNA) is described as one of the main mechanisms of SCD. In the present review, the relationship between SNA and SCD is described. A new method to measure SNA noninvasively has been developed. It consists of a frequency analysis of the time series of instantaneous heart rate (HR), and the reciprocal of the beat-to-beat interval; in other words, HR variability. HR variability is shown to result from chaos. Chaos theory is one of the most fruitful achievements of nonlinear dynamics in the last 30 years. Nonlinear dynamics is explained in detail here because it is essential for shedding light on the mechanisms of SCD. The possibility of SCD prediction based on chaos theory and an analysis of ambulatory 24-hour electrocardiogram (ECG) recordings (Holter recordings), in which ventricular fibrillation was recorded by chance, is explored. It is discussed that a V-shaped trough of the SNA change is one possible precursor of SCD. Finally, how a V-shaped trough of SNA change can be simulated by a mathematical model of HR, blood pressure (BP), and SNA is presented.

Epidemiology of Sudden Cardiac Deaths

Is it possible to predict SCD a few hours in advance of its occurrence? In the last 10 years, mass media have reported incidents in which a bus driver suffered a heart attack and a passenger who witnessed it stopped the bus. It was also reported that a runner who fainted suddenly during a full-length marathon was rescued from ventricular fibrillation with an automated electrical defibrillator. In the United States, SCD is the greatest cause of natural death, causing more than 400,000 adult fatalities per year[1]. In Japan, the number of SCD deaths is estimated to be more than 50,000 annually[2]. SCD is the most common lethal manifestation of heart disease[3]. About 5% of motor vehicle deaths are presumed to be due to the occurrence of a cardiac event in the driver that could be triggered by multiple factors[4]. This percentage may increase in the future as the number of older drivers is increasing in Japan. Hence, the high incidence of SCD makes it a major public health challenge. No reliable pre-

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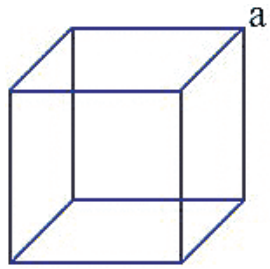

Fig. 1

cursor of SCD has yet been discovered.

Mechanisms of SCD

Some reports indicate that SNA shows a characteristic pattern a few hours before the onset of lethal ventricular arrhythmias[5–7]. Moreover, Suarez discussed the role of sympathetic stress in acute myocardial infarction[8] and Otowa et al. reported that SNA may promote coagulation through downregulation of the fibrinolytic system[9]. These findings indicate that the acceleration of SNA may be a promoter of these acute events, although it is not a main cause. Schwarz et al. demonstrated that excessive SNA could trigger ventricular fibrillation in dogs with myocardial infarction[10]. This finding is particularly notable, because this study is likely to be the first report that autonomic stress causes serious cardiac damage. In this study, SNA was measured invasively in dogs because a noninvasive method to measure SNA was not available. Finally, they reported that HR variability reflects autonomic activity. Nowadays, it is acknowledged that some measures of HR variability are clinically useful for evaluating autonomic function. A frequency analysis of the time series of an instantaneous HR yields a low-frequency component (LF: 0.04−0.15 Hz), a high-frequency component (HF: 0.15−0.4 Hz), and the ratio LF/HF, which are recognized as measures of combined sympathetic and parasympathetic activity, parasympathetic activity, and sympathetic activity, respectively[11–13]. By analyzing ambulatory 24-hour ECG recordings, we previously reported that HR and LF/HF increase steadily with a decrease in HF from 45 minutes before the onset of non-sustained ventricular tachycardia until the actual onset[14]. This suggests that increased SNA and decreased parasympathetic activity may trigger non-sustained ventricular tachycardia and also indicates that trends in autonomic activity may be useful for detecting any precursors of ventricular tachyarrhythmia that are triggered or worsened by autonomic imbalance.

What is Nonlinear Dynamics?

Is mathematics necessary for medicine? The answer is yes. Imagine looking for a treasure in the depths of a labyrinth with no map. Finding it would be a continuous process of trial and error. In contrast, if a bird's-eye view of the labyrinth was available, reaching the treasure would be easy. Similar to a bird's-eye view, the tools and ideas of mathematics are rather useful; in other words, mathematics can be used to visualize an invisible thing. Such an example is as follows. The number of ionic currents that determine the excitability of a single cardiac pacemaker cell is not clearly known yet. We determined the degrees of freedom for the excitability by chaotic analysis of a time series of action potentials recorded from a rabbit's sinus node. We provided evidence that at least 12 variables are needed to determine the action potentials. This mathematical approach to an observed time series offers a powerful tool for constructing a model for the underlying biological mechanism.

Figure 1 illustrates this concept: although the vertex of a cube (marked "a") seems to be backward at a glance, it appears to be forward when looked at again. This phenomenon shows that even when looking at the same thing, it is possible to have different perceptions. This corresponds to a transition from one phase to another mathematically. One commonly known example of phase transitions consists of the transitions between the solid, liquid, and gaseous states of water. Because the phase transitions result from nonlinear dynamics, this indicates, without the need for complicated experiments, that perception is likely under the control of nonlinear dynamics. Another well-known example is a single illustration that alternately appears to be that of an old woman or a young woman. This example suggests that there are no physical structures that correspond to an old woman or a young woman in the brain. It is presumed that a dynamic state of electrical signals (called an attractor in mathematics) corresponding to an old woman is switched to another attractor corresponding to a young woman. There is also excellent work on smell by Freeman[16].

In nonlinear dynamics, a change in the output is not necessarily proportional to a change in the input. This is expressed metaphorically as follows. When a person buys 10 apples for USD 2 per apple in a supermarket, the total cost is always USD 20. In contrast, when a regular customer at a small store buys 10 apples for the same price, the total may be only USD 18 thanks to a 10% discount courtesy of the owner. The former transaction fol-

lows linear dynamics, and the latter follows nonlinear dynamics. If I were the owner and Marilyn Monroe were a regular customer, I would offer no less than a 90% discount. Although these are rather familiar examples, they state an essential feature of nonlinear dynamics, which is that the output is customized by various conditions of the input. Another example in the circulatory system is as follows: coronary flow is constant even if coronary pressure increases within a certain range, but shifts upward when left ventricular hypertrophy occurs[17]. This means that coronary flow preserves capacity and indicates that various mechanisms of phenomena in living things involve nonlinear dynamics.

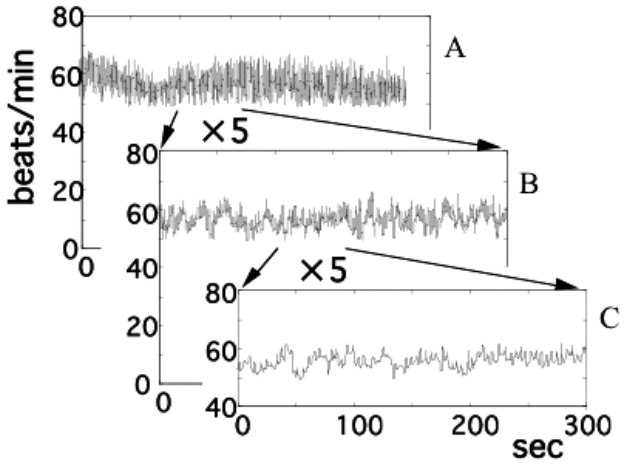

Fig. 2

Fractal, self-similarity, *1/f*-fluctuation, the butterfly effect, and chaos are popular keywords in nonlinear dynamics. Chaos theory is an interdisciplinary theory stating that although a time series resulting from a dynamical system seems to be random, in other words, "chaotic," it is deterministic and could possibility be described as a set of differential equations. Fractal, self-similarity, *1/f*-fluctuation, and the butterfly effect are contingent on chaos. **Figure 2** shows an example of the fractal nature (i.e., self-similarity) of HR dynamics. A graph of an instantaneous HR is taken from an ECG recording of a healthy man (myself) over 125 min (**Fig. 2A**). Even if an arbitrary part of it is expanded five times (**Fig. 2B**), the pattern of fast fluctuations superimposed on a slow fluctuation seen in **Figure 2A** appears in **Figure 2B** as well. Moreover, even if an arbitrary part of **Figure 2B** is expanded five times (**Fig. 2C**), a similar pattern appears. This indicates directly that HR variability in a normal state has a fractal nature (self-similarity). **Figure 3A** shows an important example of fractals in nature. Seaweed (*isohagi* in Japanese) shows a typical fractal structure: a branching pattern seen in the whole leaf appears in the smaller parts as well. Such a pattern can be simulated by a mathematical model called the "Dancing J," which consists of three ordinary differential equations (**Fig. 3B**). This suggests that, although the fractal image seems to be rather complicated, it is presumed to result from a simple rule. The fractal nature of the instantane-

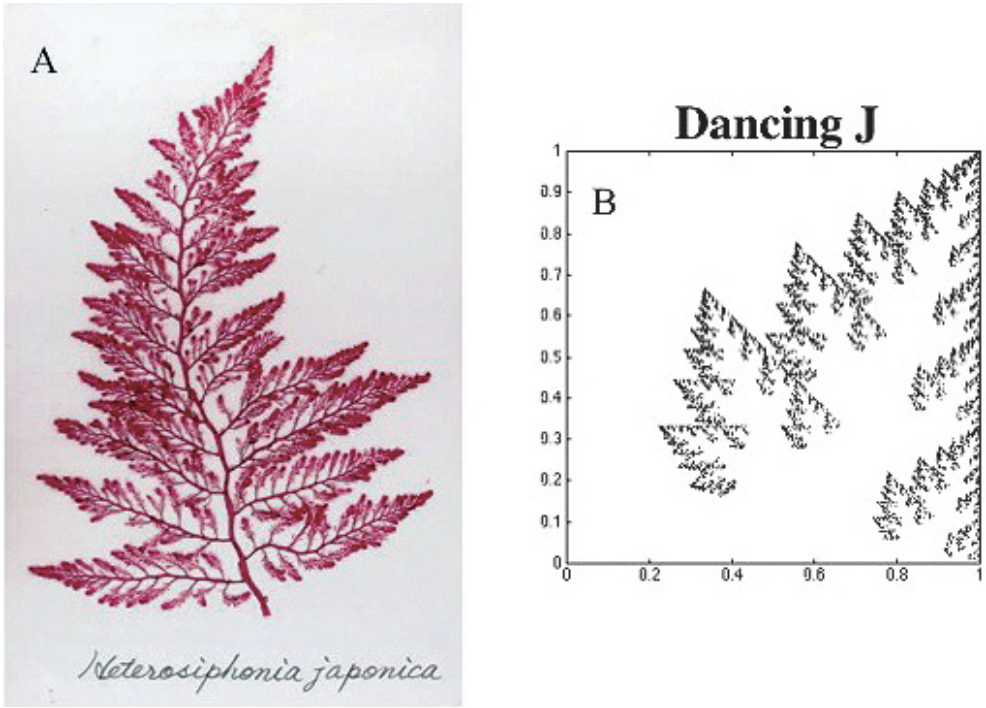

Fig. 3

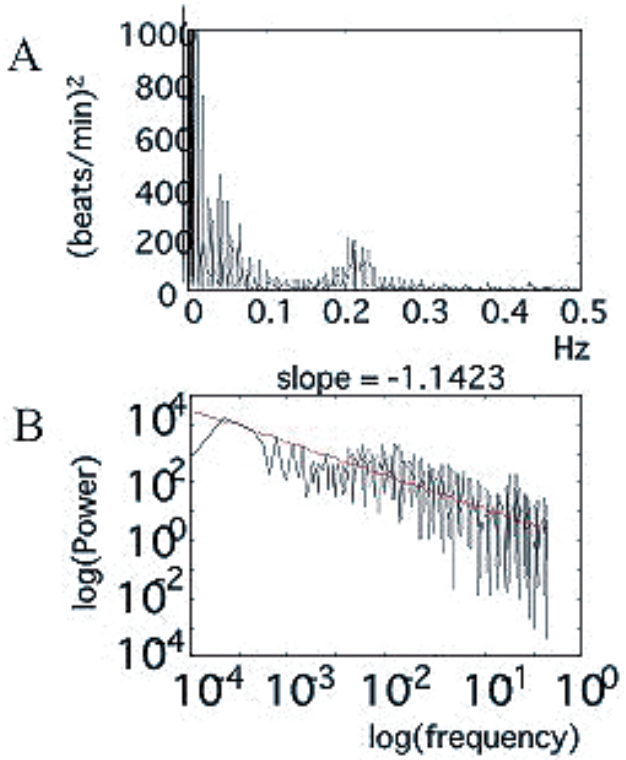

Fig. 4

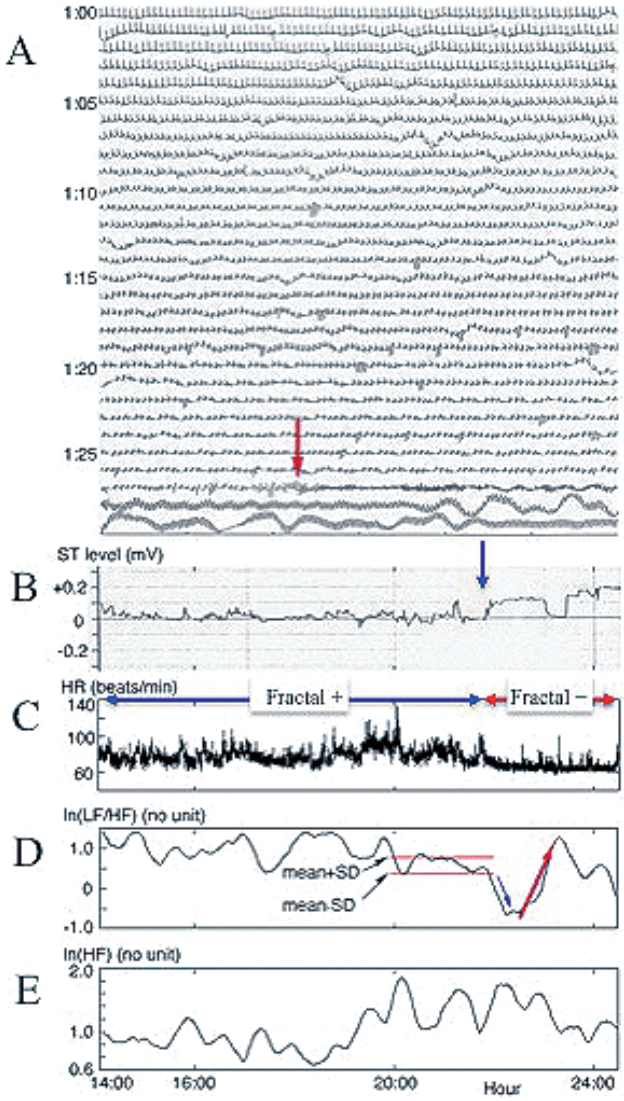

Fig. 5

ous HR graph (**Fig. 2**) indicates that HR dynamics may result from a simple rule. We have demonstrated that HR dynamics result from low-order chaos (at most 5-dimensional chaos), which indicates that HR dynamics might be described by no more than five ordinary differential equations[18].

Chaotic Nature of HR Variability

The power spectra of HR from healthy individuals have a *1/f*-like pattern ($Power=Cf^{b}$, where $b \approx -1$ and C is a proportionality constant) in the low-frequency range ($f<$ 0.1 Hz) (**Fig. 4**)[19,20]. This results from the fractal nature of HR. It was shown that loss of multifractality is closely correlated with the prognosis and severity of heart disease[21]. Bigger et al. reported that a steeper slope of the *1/f*-like pattern is an excellent predictor of death after myocardial infarction[22]. Although the mechanism remains unknown, despite its clinical significance, it is presumed that the low-frequency component is strongly correlated with the prognosis.

Precursor of SCD

The aim of our research was to find a precursor of a lethal cardiac event by examining ambulatory 24-hour ECG recordings in which such a spontaneous event had been recorded[23]. Although no reliable precursor of SCD has yet been discovered, we recently found a possible precursor. The 24-hour ambulatory ECGs of 23 patients in which ventricular fibrillation was recorded by chance (Event-group, 14 deaths) were compared with 191 controls (No Event-group). **Figure 5A–E** show a representative case in the Event-group[23]. The patient (male, 72 years old) suffered from an acute myocardial infarction and died of ventricular fibrillation during the recording. **Figure 5A** shows the progression from a regular sinus rhythm to ventricular fibrillation (red arrow) with sporadic short runs of ventricular tachycardia. In **Figure 5B**, a sustained ST elevation appears at 21:50 (blue arrow), indicating the occurrence of acute myocardial infarction. Note that thereafter, slow oscillations of the HR seem to disappear and their variability is depressed (**Fig. 5C**). This depressed HR variability corresponds to a loss of fractality, which is closely correlated with the severity of heart disease[21]. The variation of ln(LF/HF) decreases

from 20:00 to 22:00, and lies approximately within the mean±SD (**Fig. 5D**). This decrease appears before the ST elevation. Next, ln(LF/HF) falls steeply and then rises sharply. **Figure 5D** shows a V-shaped trough in the SNA, which is referred to simply as a "V-trough." Although such a sharp rise of ln(LF/HF) and a simultaneous decrease of ln(HF) (**Fig. 5E**) would normally be expected to accompany an increase in HR, there is instead a decrease in HR that is accompanied by a reduction in variability (**Fig. 5C**). Slow ventricular tachycardia appears at 0:30 and ceases at 0:50, then ventricular fibrillation appears at 1:27, terminating in cardiac standstill at 1:55.

A V-trough appeared in the LF/HF curve, which represents the trend of the SNA, before such an event in 20 patients of the Event-group (**Fig. 5D**). The V-trough was marked by a small variation lasting 2 hours, an abrupt descent lasting 30 minutes, and a sharp ascent for 40 minutes. The criteria for a V-trough were defined mathematically to automatically determine if a V-trough has occured[23]. The sensitivity and specificity of an LF/HF V-trough for predicting ventricular fibrillation are 87% and 95%, respectively. We found that LF/HF did not change monotonically but as a V-shaped trough before ventricular fibrillation. Our next task was to determine if such a phenomenon could be simulated using a mathematical model.

Mathematical Model of HR Dynamics

We sought to make a mathematical model of the system that meets the three experimental findings: 1) the SNA peaks precede the HR peaks and BP nadirs[24], 2) the power spectra of the HR shows a *1/f*-like relationship between frequency and power[19,20], and 3) the HR exhibits low-order chaos[18]. Based on the conclusion that our system of interest is chaotic in nature, we modeled the system after a known chaotic electrical circuit, the Chua circuit[25,26]. The advantages of this approach are that mathematical notation can be replaced by concrete elements with familiar behaviors and that analogies can be drawn between the system of interest and the circuit elements. The circuit dynamics are described by three ordinary differential equations:

$$\frac{dx}{d\tau} = \alpha(y - x - f(x))$$

$$\frac{dy}{d\tau} = x - y + z$$

$$\frac{dz}{d\tau} = \beta(-y - \gamma z),$$

where $f(x) = bx + \frac{a-b}{2}(|x+1| - |x-1|)$.

In this dimensionless system, x, y, and z correspond to HR, SNA, and BP, respectively.

The power spectrum of x shows a *1/f*-like power law scaling between 0.0005 and 0.02 Hz. The slope increases from −1.32 (γ=*0.001*) to −1.53 (γ=*0.002*). Inspection of the differential equations suggests that an increased γ implies that the BP sensitivity to change in the SNA is decreased. This is entirely consistent with the fact that reduced interaction between BP and SNA contributes to the maintenance of hypertension in spontaneously hypertensive rats[27,28]. It indicates that the increase of γ, in other words, a reduced interaction between BP and SNA, causes a steeper slope in spontaneously hypertensive rats. The results of the simulation by the modified Chua circuit meet all three experimental findings. Bigger et al. reported that a steeper slope correlates with a poor prognosis of patients with postmyocardial infarction[22]. Although the mechanism is unknown, our findings suggest that impaired regulation of the BP by SNA may be closely correlated with the prognosis. Such a depressed sensitivity was considered to cause lethal ventricular tachyarrhythmia in conscious transgenic mice with cardiac $G_{s\alpha}$ overexpression[29].

Simulation of the V-trough by the Modified Chua Circuit

The parameter settings of the modified Chua circuit were fixed as follows: α=*15.6*, β=*30*, *a*=−*8/7* and *b*=−*5/7*, and seven 1-second time steps were taken[25]. Although a V-trough in the low-frequency component of $y(\tau)$, which corresponds to SNA, did not appear at γ=0.0015 and 0.002 (this range corresponds to a normal state), a V-trough appeared at γ=0.0025 (corresponding to a pathological state of reduced interaction between SNA and BP)[25].

Potential Tools to Prevent SCD

The clinical and experimental findings are summarized as follows: 1) an excessive predominance of SNA over the parasympathetic nerve activity with reduced interaction between SNA and BP may trigger lethal ventricular tachyarrhythmias[10], 2) the modified Chua circuit for HR, SNA, and BP can simulate a steeper slope when the interaction between SNA and BP is reduced, 3) this reduced interaction is considered to cause the steeper scaled slope of the HR in patients with postmyocardial infarction[22] who have a poor prognosis, 4) this circuit can

simulate a V-trough in the SNA, which may be a precursor of SCD because of lethal ventricular tachyarrhythmias when the interaction between SNA and BP is reduced.

We reported that SNA precedes HR and BP in all normotensive and hypertensive rats[24]. We calculated the value of mutual information between each pair of these parameters, which quantifies both the linear and nonlinear correlations between two variables. We had previously determined the threshold between correlated and non-correlated data to be 0.047[30]. The values in these data were above the threshold (0.14±0.06 between SNA and HR; 0.11±0.05 between SNA and BP), indicating a strong correlation between SNA and the other variables. Mutual information can also be used to quantify temporal relationships between variables[30]. Our calculations show that SNA peaks precede HR peaks and BP nadirs. We interpret this result as an indication that slow oscillations of the HR and BP are produced by slow oscillations of the SNA. The usual physiological interaction between the BP, HR, and SNA is known as the baroreflex, wherein an increase in BP is compensated for by decreases in HR and vascular resistance, or vice versa,, mediated by SNA emanating from a reflex center in the brainstem. In other words, the BP drives SNA. This response of SNA to BP is fast, that is, it is a beat-to-beat response. In contrast, we found that the low-frequency components of SNA precede those of HR and BP. Thus, correlation in the low-frequency band (<0.1 Hz) is different from the beat-to-beat control. Although the origin of the slow oscillation of SNA remains unknown, we presume that the physiological location of the "resistive element" may be rostral ventrolateral medulla (RVLM) neurons, which are located at a pivotal site involved in the baroreflex pathway and play an important role in controlling peripheral SNA. Kumagai et al. reported the following findings: 1) The neurons in the VLM have a role in SNA and BP control using the optical imaging in the brain stem-spinal cord preparations of neonatal spontaneously hypertensive rats (SHRs)[31]. 2) The responses of RVLM neurons to angiotensin II and the angiotensin II type 1 receptor antagonist candesartan differ between neonatal Wistar-Kyoto rats (a model of normal BP) and SHRs[32]. 3) Candesartan improves the impaired baroreflex in conscious rats with congestive heart failure[33]. We reported that the SNA value in SHRs given candesartan orally for two weeks was significantly lower than in SHRs given vehicle, despite the lower BP[24]. Therefore, we believe that a long-term oral treatment with candesartan is one potential tool for preventing SCD by improving the impaired regulation of BP by SNA.

There is a case report on the recurrence of cardiac arrest immediately after delivery[34]. It suggests that a certain functional promoter is related to the recurrence of cardiac arrest and might be a surge of SNA, which might occur repeatedly. An implantable cardioverter defibrillator (ICD) is implanted into patients who have experienced syncope due to ventricular fibrillation for preventing such an attack. During regular medical checks (for example, twice a year) of the recordings in the ICD, some of the patients were found to have had a few attacks of ventricular fibrillation that had been suppressed by the defibrillator. These findings indicate that ventricular fibrillation occurs sporadically and when it appears is unknown. This unpredictability is considered to be due to chaotic dynamics that can be simulated using the modified Chua circuit. The simulation using the modified Chua circuit suggests that there is a risk of SCD in patients showing loss of fractality of HR variability after acute myocardial infarction. Hence, implantation of an ICD for such a patient is another potential tool for preventing SCD.

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Conflict of Interest: The author declares that there is no conflict of interests regarding the publication of this paper.

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