evaluated the comorbidity of PD with heart disease and the prevalence of PD in 128 out-patients presenting to a cardiologist. They found that 16 patients (12%) met the criteria of PD, and 73 (57%) were shown to have actual cardiac illness; of these, 10 (14%) had PD (Morris et al. 1997). In a prospective study of 33,999 males, the risk of sudden cardiac death was significantly related to anxiety: a multivariate odds ratio of 2.96 (95% CI: 1.02–8.55) for males who scored 1 on the Anxiety Symptom Scale compared with males who scored 0, and 4.46 (95% CI: 0.92–21.6) for males who scored 2 or higher (Kawachi et al. 1994a, 1994b). Thus, there are many findings of significant relations between PD and CVD for male patients at least. However, the pathology is unclear (Jakubec and Taylor 1999).

It is well established that impaired autonomic nervous system (ANS) control of heart rate (HR) such as low HR variability predicts cardiac mortality (Kleiger et al. 1987; Molgaard et al. 1991; Odemuyiwa et al. 1991; Bigger et al. 1993; Watkins et al. 1999). In particular, reduced baroreceptor-mediated vagal reflex control of HR has been associated with life-threatening arrhythmias (Hohnloser et al. 1994; De Ferrari et al. 1995) and fatal cardiac event in patients (Farrell et al. 1991; Osterziel et al. 1995; La Rovere et al. 1998).

Under these circumstances, since the late 1980s a number of studies have attempted to investigate the abnormalities of ANS in PD using methods such as power spectrum analysis of HRV, but the results are controversial (Ito et al. 1999; Fleet et al. 2000; Gorman and Sloan 2000; Jeejeebhoy et al. 2000; Rao and Yeragani 2001; Yeragani et al. 2002). Some of the reasons for this controversy may be due to the fact that most of these conventional studies have analyzed each physiological variable independent of other indices (Yoshizawa et al. 2001) and the differences in pathological states of PD patients (Stein and Asmundson 1994; Seier et al. 1997; Ito et al. 1999).

From the perspective of relapse prevention, we hypothesized that there might be some abnormalities of ANS during periods of remission in remitted patients with PD. In this study, to clarify this hypothesis we used power spectrum analysis of HR variability as a usual and a new method which can more directly investigate the function of the baroreflex by examining the relation between the blood pressure (BP) and HR before and after audiovisual stimulations (AS) (Yoshizawa et al. 2001).

Subjects and methods

Subjects

The subjects were 13 male out-patients (mean ± SD age, 35.1 ± 6.6 years) who had been diagnosed as having PD according to DSM-IV criteria (American Psychiatric Association 1994). None of the patients had any comorbidity with depression, and all of them were examined after they had been in the remission phase of PD, defined as the absence of any major panic attack symptoms and agoraphobia, for at least 6 months preceding the measurement. All were receiving regular out-patient treatment including medications at the Psychiatry Clinic of the Niigata University School of Medicine Hospital. None of them was found to have any past history of head injury, neurological disorders, drug or alcohol abuse, or serious medical illnesses. Only 5 patients (38%) were treated with paroxetine (10–40 mg/day) or fluvoxamine (50–150 mg/day) and irregularly used alprazolam.

Twenty mentally and physically healthy control subjects (NC; 36.0 ± 6.5 years), who were age and gender matched with individual patients, were selected from among a group of volunteers. All control subjects were in good physical health, and none of them had any notable history of mental disorder, neurological disease, head injury, or substance dependence, or any family history of mental disorder or substance dependence.

The psychiatric state of each patient on the day of the examination was assessed using the Sheehan patients-rated Anxiety Scale immediately before the measurement (SAS; Sheehan 1986). There was a significant group difference in SAS (*PD group*: 64.6 ± 19.9, *NC group*: 36.5 ± 2.8, $t = 3.97$, $p < 0.002$), but not in age and gender. To check their physical and mental states after the AS, simple questionnaires including 13 questions were given to all subjects, such as "Is general physical condition worse?", "Do you have headache?", "Are you less comfortable?", " Are you tired?", and so on.

Audiovisual stimulation (AS)

In this study, we used AS as a mental load including psychological stress, which must change the autonomic nervous activity and the relation between BP and HR. Subjects were exposed to video images recorded using a camera mounted on a motor vehicle such as a kart, car, motorbike, mountain-bicycle, bobsleigh or motor vessel such as a jet boat with simultaneously recorded sounds, and computer graphics such as moving balls for 17 minutes. In the middle of the video playback, they watched a scene of a tropical sea for 40 seconds as relaxation. Before and after loading the AS, 5 minutes of rest was allowed for each subject.

Images were back-projected onto an 80-in screen. Subjects sat in a chair 2 meters from the screen with a comfortable posture. Two LCD projectors (XGA, TH-L795J, Panasonic, total of 1,400 lumens) aligned together were used. Environmental conditions in the examination room were kept constant (temperature: 22 °C, intensity if illumination: 10 lux) and the time of AS was constant (16:00–17:00). The method of AS was basically similar to that described previously (Kojima et al. 2002, 2004). This study was approved by the ethical committee of Niigata University Graduate School of Medical and Dental Sciences.

Measurements and data analysis

The left radial arterial pressure signal acquired using a tonometoric pressure sensor (Nihon Corin; JENTOW 7700, JAPAN) and the ECG signal were sampled by using a data collection system (LabView, National Instruments Co., TX) and also stored on a digital tape every 1 ms. Mean blood pressure (P_{mean} [mmHg]) was obtained as the mean value of the radial arterial pressure signal over the heart beat. Heart rate (HR[min^{-1}]) was calculated from the reciprocal of the inter-R-wave interval of the ECG signal.

Each beat-to-beat variable P_{mean} and HR was interpolated by the cubic spline function to be a time-continuous function, and the function was re-sampled every $\Delta t = 469$ ms (128 points per minute). For 2 min of the 5-minute rest period before and after AS, the power of HR was calculated using the Fourier transform (256 points) on the basis of 2 min data segmented by the Hanning window from -1 min to 1 min. The low frequency (LF), high frequency (HF), and ALL were defined as the sum of the components of 0.039–0.159, 0.176–0.508 and 0–1.016 Hz, respectively. The %LF and %HF were defined as {100×(LF/ALL)} and {100×(HF/ALL)}, respectively (Yamamoto and Hughson 1991; Montano et al. 1994; Ando et al. 2002).

Each of the re-sampled P_{mean} and HR data were normalized as the mean = 0 and variance = 1, respectively. Then, they were filtered through a band-pass filter with a bandwidth between 0.08 Hz and 0.1 Hz to extract the Mayer wave component, which is a measure of a response of the ANS to psychological excitement (Akselrod et al. 1985;

Pagani et al. 1986; Baselli et al. 1988; Oka et al. 1995). For 2 min of the 5-minute rest periods before and after AS, the mean lag time (τ) of the Mayer wave components between variabilities of P_{mean} and *HR* was calculated on the basis of 2 min data segmented by the Hamming window from −1 min to 1 min (see Fig. 1).

Statistical analysis

To determine whether significant differences in the power spectrum analysis and the τ existed between the groups and/or the time (before/after AS), a two-way analysis of variance (ANOVA) with random effect was performed after logarithmic transformation. Moreover, in order to analyze the relation between clinical anxiety symptoms and the τ, we used Pearson's correlation coefficient. Values are expressed as means ± S. D. A probability level of $P < 0.05$ was regarded as statistically significant. The data were analyzed using the statistical software SPSS (release 10.07J, SPSS).

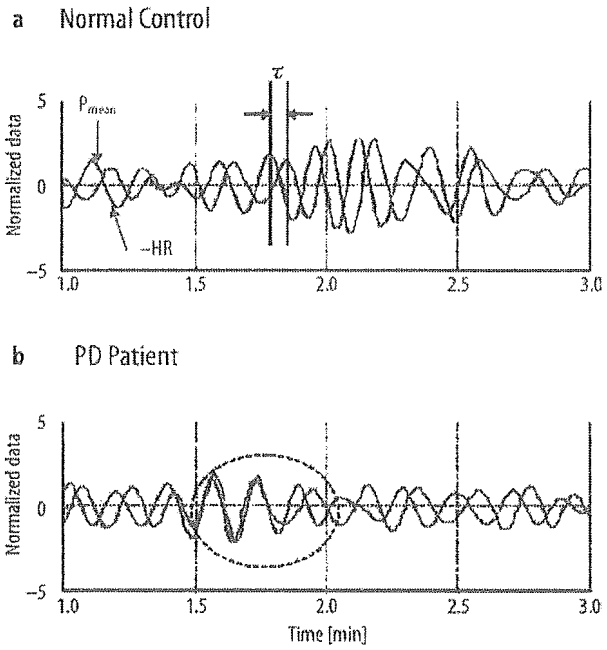

Fig. 1 Mayer wave components of P_{mean} and *HR* before audiovisual stimulation (AS) in a representative subject in each group. **a** The Mayer wave components of P_{mean} and *HR* before AS in a normal control. As for HR components, the minus sign shown in −HR was introduced to become as in phase as possible for simple interpretation. The τ is defined as the mean lag time (phase difference) of the Mayer wave components between P_{mean} and *HR*. The τ values in a normal control are constant before AS (about 3 s). **b** These waves show the representative Mayer wave components of P_{mean} and *HR* in PD patients before AS. The τs are fluctuated and the mean of τ values are about 2 s as indicated by the dotted line area where the phase differences were changed

Results

No subject in either group had any panic symptoms during the AS or noted a dislike for the AS, for example "never try it again". Table 1 shows the results of power spectrum analysis for the HR. The two-way ANOVA showed that there were no significant group or task differences, but a mild significant interaction for LF/HF ($F = 4.18$, $P = 0.049$).

Fig. 2 shows differences in τ between the PD and NC groups before and after AS. The two-way ANOVA revealed that there was a significant group difference in τ ($F = 8.35$, $P = 0.007$) and a significant interaction between the group and task ($F = 7.91$, $P = 0.008$). Before the AS, there was a mild significant correlation between SAS total scores and the τ ($R = -0.35$, $p = 0.045$) in all subjects, but not after the AS ($R = -0.10$, $p = 0.574$). However, in the PD group we could not confirm this correlation for either condition. No τ was significantly correlated with age at onset, duration of illness or medication.

Discussion

In this preliminary study, using ECG and a tonometoric pressure sensor we first tried to investigate more di-

Table 1 Power spectrum analysis of the *HR* in PD and NC groups

ANS Parameter	Before/After Audiovisual Stimulation	Groups	
		PD	NC
%LF	Before	51±18.5	54±18.6
	After	51±12.3	57±15.6
%HF	Before	0.21±0.23	0.17±0.13
	After	0.16±0.07	0.14±0.12
LF/HF	Before	5.4±3.5	5.9±4.7
	After	4.4±2.8	9.0±7.9

PD patients with panic disorder; *NC* normal controls; *LF* low frequency; *HF* high frequency
The two-way ANOVA showed that there were no significant group or task differences, but a mild significant interaction for LF/HF ($F = 4.18$, $P = 0.049$)

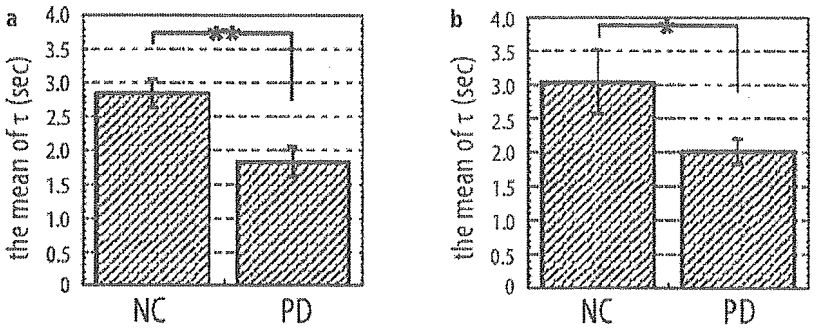

Fig. 2 Differences in τ between the PD and NC groups before (**a**) and after (**b**) AS. The ordinate and abscissa indicate the levels of the mean τ (per second) and the groups, respectively. The two-way ANOVA shows that there is a significant group difference in τ ($F = 8.35$, $P = 0.007$) and a significant interaction between the group and time ($F = 7.91$, $P = 0.008$). Using the Mann-Whitney U test, there are significant group differences before and after the AS (before; $Z = -2.78$, $P = 0.004$: after; $Z = -2.07$, $P = 0.039$)

rectly the relation between two physiological variables, BP and HR, to assess the cardiovascular ANS in PD.

In the present study, we found that there were significant group differences in τ before and after AS. Unfortunately, we cannot directly compare the present results with those of any other pathophysiological study in PD since to our knowledge this is the first study to use the new method mentioned above. In this study, τ was defined as the mean lag time of the Mayer wave components between P_{mean} and *HR*. Thus, for the new analysis, we used only this component which is closely related to sympathetic nerve activity of vasomotor (Oka et al. 1995) because of the following reasons; a) Faravelli and Paionni reported that almost all physical symptoms are due to the activation of the sympathetic nervous system because of many previous findings in PD such as elevated plasma and urinary concentrations of adrenaline, noradrenaline and their metabolites (Charney et al. 1984a, b; Ko et al. 1983), and increased activity of platelet monoamine oxidase and reductions in the number of β and α receptors (Cameron et al. 1984; Faravelli and Paionni 1999), b) in normal subjects mental stress increases plasma epinephrine and norepinephrine and HR increases markedly (Opie 1998), and c) psychological excitement can raise the dominant response in the Mayer wave component (Akselrod et al. 1985; Pagani et al. 1986; Baselli et al. 1988).

It is suggested that the τ used in the present study may become an index to detect subtle changes of cardiac sympathetic nerve function compared with usual methods because τ is a value measuring more directly the correlations between the HR and BP, while the power spectrum analysis uses only one parameter such as the R-R interval.

We hypothesized that τ would be normal before the AS and become shortened after the AS because remitted PD patients nevertheless must have an unstable ANS, especially cardiac sympathetic nerve function. In the present study, however, we found that τ in the PD group was significantly shorter than that in the NC both before and after AS, especially before. Fig. 1 shows that in the NC group the phase differences of the Mayer wave components between the HR and BP were constant (about 3 seconds), while in the PD group they were shortened in part. It is suggested that the baroreflex regulation is accurately functioning when the phase differences are constant and about 3 seconds as in the NC subjects. Thus, even during periods of remission PD patients may have dysfunctional baroreflex regulation of sympathetic nerve activity. Moreover, this finding may suggest the high rate of relapse in PD, especially after pharmacological treatment (Noyes et al. 1989; Otto and Whittal 1995; Pollack and Smoller 1995; Pollack 1998; Oakley-Browne 1999; Gorman et al. 2000), and higher cardiovascular mortality in this group (Coryell et al. 1982, 1988). To confirm this, we continue to observe the long-term outcomes for all patients that participated in this study under drug-free conditions.

The reasons why the τ in the PD group was constantly shorter before and after the AS are unclear. Recently, Cohen et al. (1998), who studied patients with post-traumatic stress disorder (PTSD), suggested that PTSD patients whose basal autonomic state was characterized by increased sympathetic and decreased parasympathetic tone demonstrated no autonomic response to the recounting of the triggering stress event (Cohen et al. 1998). In Griffin's study, there was also a suppression of autonomic physiological responses in the PTSD group (Griffin et al. 1997). Although these were PTSD studies, it is possible that patients with PD, which is also an anxiety disorder category similar to PTSD, have diminished autonomic response to stress. Further studies are needed to investigate the differences in autonomic functions between PD and PTSD. More recently, Lautenbacher (2002) investigated the discrimination between left and right visual field stimulus processing in drug-free patients with PD and concluded that PD patients appeared as disturbed in their attentional functioning (Lautenbacher et al. 2002). We are in the planning state to investigate the relationship between the abnormalities of ANS such as our finding and the central nervous system such as attention and recognition.

In this preliminary study there are a few limitations as follows. First, the sample size was relatively small, although three-fifths or greater than 50 previous studies had a similar sample size (see review; Friedman and Thayer 1998; Gorman and Solan 2000; Jeejeebhoy et al. 2000). Second, it is possible that the response to the AS in our remitted patients with PD may be due to a hyperanxious state because of the higher SAS total score in the PD patients compared to the NC and because of a mild significant correlation between SAS total scores and the τ before the AS. However, this significant correlation vanished if the NC group was excluded from this analysis since the distribution of the SAS total score shifted to the lower range compared with the PD group. Third, we could not remove the medication effects from our results completely. To confirm the present findings, as mentioned above, additional studies in drug-free patients are needed. Fourth, we could not use a video which triggered the special fears of PD patients in this study. Finally, it remains unclear whether this finding for τ is specific for PD. Therefore, it is necessary to study other anxiety and/or mood disorders using this new method.

In conclusion, we found dysfunctional baroreflex regulation of sympathetic nerve activity in remitted patients with PD using a new method. The present results may be relevant to the higher risk of relapse and cardiovascular mortality in this group. It is suggested that this new technical approach is available to measure the autonomic function in other psychiatric disorders such as PTSD, generalized anxiety disorder, social anxiety disorder, specific phobia, and depression.

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脳と心による心臓の制御

4

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YAMBE Tomoyuki, NITTA Shin-ichi/東北大学加齢医学研究所病態計測制御研究分野

近年，心臓血管系の圧反射系としての解析が進み，その基本的な動特性がかなり簡単な線形システムとして表せることがわかってきた．しかし，心臓血管系には，心拍数変動や血圧変動に含まれるいくつかのゆらぎ成分や，心理的ストレスなどに対する情動反応のような複雑な様相も存在する．本稿では，心臓血管系の基本特性が単純であるにもかかわらず，情動反応や非線形性・非定常性のような複雑な性質が存在することに関して，自然心臓による循環制御と人工心臓による人工的循環制御を対比させながら解説する．さらに，心理的状態を循環系パラメータ間の相関性で定量化する試みについても紹介する．

Key words
心臓血管系
情動反応
循環制御
システム同定
人工心臓
自律神経

はじめに

心臓の主たる機能は，血液を体内に循環させるポンプ機能である．にもかかわらず，古来，心は心臓に宿るという見方がなされてきた．このような見方がなされてきた理由は，人の心を表す喜怒哀楽や精神的緊張を反映して心拍数や血圧などが大幅に変動すること，すなわち，情動反応[1]が心臓血管系に現れるというところにあると思われる．

逆に，このことを利用することにより，心拍数や血圧などの循環系パラメータを計測することによって，人間の感情や精神的ストレスを推定しようという試みがなされてきた[2)-5)]．しかし，そのような試みは，循環系パラメータが持つ複雑なゆらぎ，再現性の低さや大きな個人差に阻まれて，決定的な方法はまだ十分に得られていない．

一方，心臓血管系の血圧反射系としての解析が進み，その動的システムとしての特性が定量的に明らかになりつつあり，その特性はかなり単純な線形システムとして表せることがわかっている[6)]．

本稿では，心臓血管系の動的システムとしての基本的な特性が単純であっても，情動反応や非線形性・非定常性のような複雑な性質があるという矛盾に関して，自然心臓による循環制御と人工心臓による人工的循環制御を対比させながら解説する．さらに，心理的・精神的状態を循環系パラメータ間の相関性で定量化する試みについても紹介する．

循環制御系の神経生理学的機能と動的システムとしてのモデル化

1．循環制御の種類と基本的な機能

心臓の循環制御は主に次の3つでなされている[7]．

i）自己調節
ii）体液性調節
iii）神経性調節

i）の自己調節は，静脈還流量が多いほど心室がより膨らみ，それに応じてより強い張力が発生し血液を強く押し出すという，スターリングの法則に基づいた調整機能であり，心筋自体の物理的特性によるものである．ii）の体液性調節は，血中の内分泌物質による調節である．自律神経が離断されている移植した心臓においても運動時に心拍出量が上昇するのは，脳からの指令で増加した血中カテコールアミンによって，心臓の収縮力と心拍数が増加するためである．iii）の神経性調節は，次に述べるような自律神経系による作用である[8]．

自律神経は，交感神経と副交感神経の2つの拮抗的な神経系からなる．これらのうち心臓交感神経は，ノルアドレナリンを神経伝達物質として分泌し，これが心臓側のβアドレナリン作動性受容体に作用して，心臓の収縮力と心拍数を増加させる．これに対して，心臓迷走神経はアセチルコリンを分泌し，コリン作動性受容体の作用でその亢進が心拍数を減少させる．一方，交感神経が血管に対する作用は，血管の種類に応じて相反する（地域性反応）．すなわち，内臓などに分布する交感神経終末から放出されるノルアドレナリンは血管を収縮させるのに対して，骨格筋に分布している交感神経終末から放出されるアセチルコリンは血管を拡張させる．このような相反的な作用は，運動時に内臓への血流を減らし，骨格筋への血流を増加させるように働く．

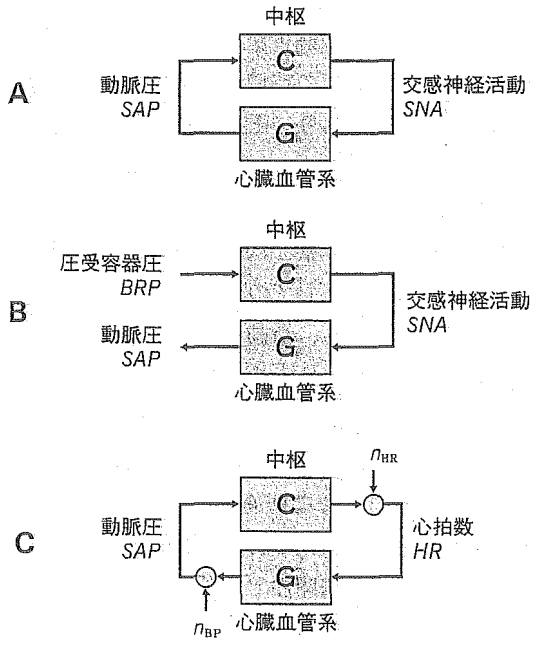

図1　循環制御系の最も簡単なモデル
（文献6より一部改変引用）

2．循環制御系の最も簡単なモデルとその同定

ところが，上述したような基本的な神経生理学的機能を個々に明らかにしていっても，循環制御系の全体像を理解することは難しい．循環制御系全体の動的ふるまいを定量的に理解するには，制御工学的表現が有用である．ここで制御工学的表現とは，システムの出力を目標値に近づけることを目的としたシステムの数学的記述のことである．

循環制御系の最も簡単なモデルは，図1Aのように表すことができる[6]．同図は，循環制御系が，動脈圧*SAP*を入力とし交感神経活動*SNA*を出力とするサブシステムである圧反射中枢*C*と，*SNA*を入力とし*SAP*を出力とするサブシステムである心臓血管系*G*が互いに結合した閉ループ系であることを表している．制御工学的には*G*が制御対象であり，その出力である血圧*SAP*を目標値に近づけるように，制御装置*C*は交感神経活動*SNA*を出

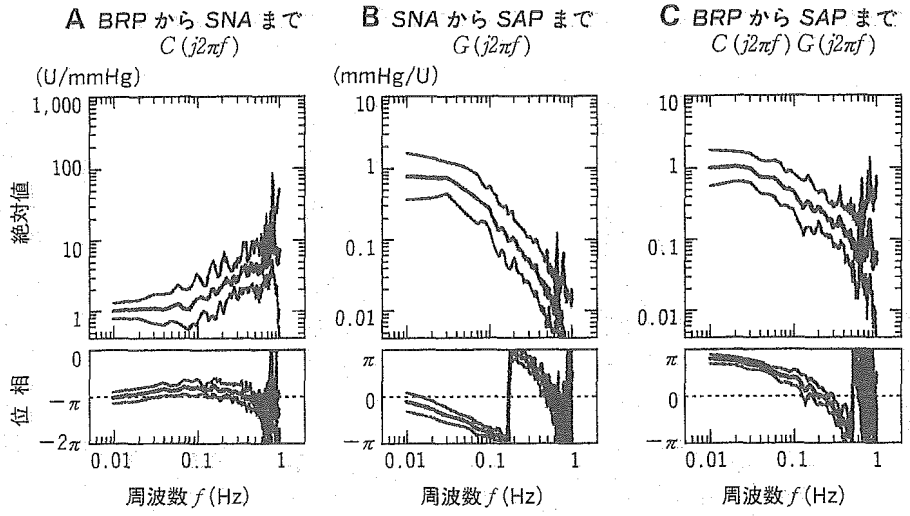

図2　ウサギの圧反射系の周波数特性(12羽の平均)
(文献6より引用)

力する．これがGへの入力(操作量)となる．すなわち，この系はフィードバック制御を行っている．

問題はどのようにしてCとGを数学的に記述するかである．このような作業はシステム同定と呼ばれている．図1Aのような系を，ループを閉じたままで正確に同定することは困難であることが数学的に明らかになっている．かといって，生体においてループを安易に切るわけにはいかない[9]．

Sunagawaら[6]のグループでは，図1Bのようなループを開いた状態で，かつ，心臓を生かしたままのシステムを人為的に作り，CとGをそれぞれ同定している．彼らは12羽のウサギにおいて頸動脈内の圧受容器の圧力*BRP*を人為的にランダムに変化させ，その時の心臓交感神経の活動*SNA*を計測した．一方，心臓交感神経をランダムに電気刺激した時の体動脈圧*SAP*を計測した．その後，*BRP*から*SNA*までの周波数特性$C(j2\pi f)$および*SNA*から*SAP*までの周波数特性$G(j2\pi f)$を，それぞれの計測量のフーリエ変換から求めた．ここでjは虚数単位であり，f(Hz)は周波数である．その結果は図2A，2Bのようになり，$C(j2\pi f)$の平均値はむだ時間要素e^{-Lcs}を持つ1次進み系の伝達関数

$$C(s)=-(1+sT)e^{-Lcs}$$
$$T=(2\pi f_c)^{-1}\ ;\ f_c=0.12\text{Hz}\ ;\ L_c=0.55\text{s} \quad \cdots\cdots(1)$$

で近似でき，$G(j2\pi f)$の平均値はむだ時間要素e^{-LGs}を持つ2次系の伝達関数

$$G(s)=\frac{\omega_n^2}{s^2+2\zeta\omega_n s+\omega_n^2}e^{-LGs}$$
$$\omega_n=2\pi f_G\ ;\ f_G=0.071\text{Hz}\ ;\ \zeta=1.37\ ;\ L_G=1\text{s} \quad \cdots\cdots(2)$$

で近似できるとしている[10]．ここで伝達関数とは，入力のラプラス変換に対する出力のラプラス変換の比であり，$s=j2\pi f$と置き換えると周波数特性に等しくなる．図2Cは*BRP*から*SAP*までの周波数特性($C(j2\pi f)G(j2\pi f)$に相当)である．CとGは注目する周波数範囲で十分な線形性を持つことも示されている[10]．

図2Bは制御対象$G(s)$が遮断周波数0.07Hzより高い周波数成分が急激に減衰することを意味している．また，$C(s)$と$G(s)$を合わせたむだ時間L_C+L_Gは約1.6秒であり，骨格筋の運動

制御系などと比べるとかなり長い．圧受容器反射を司る$C(s)$が高周波領域で微分特性(両対数グラフにおける絶対値の傾きが1すなわち20dB/decade)を持っている理由は，長いむだ時間を持ち低域通過特性の強い制御対象を，安定性を保ちながら帯域幅を拡大し応答速度を改善するためであると解釈されている[10]．

2 循環制御系の複雑さ

上述のように，ウサギの循環系は，(1)，(2)式のようなかなり簡単な線形システムで表されることが明らかになった．しかし，これだけで循環系の中身がすべて表されたわけではない．すなわち，このような簡単なモデルには次のような難点がある．

1）静特性の変動が考慮されていない．
2）ゆらぎ成分を表現できない．
3）非定常性(時変性)や非線形性を表現できない．
4）人工心臓の制御則を与えてくれない．

1．静特性の変動

1）の静特性とは，*BRP*に対する*SNA*の変化が逆S字状(減少関数)であり，*SNA*に対する*SAP*の変化がS字状(増加関数)であることである．この2つの曲線の交点で動作点が決まる[6]．(1)，(2)式の動特性は，この動作点周りだけの特性を表している．Yamamotoら[11]は，ウサギにおいて骨格筋の筋張力を変化させると*SNA*-*SAP*特性はあまり変化しないが，*BRP*-*SNA*特性が*SNA*を増加させる方向に移動することを報告している．これは，運動時には交感神経活動が高まることを示唆するものである．したがって，安静状態から運動状態へ移行するような過渡状態を正しく表すためには，静特性のシフトと動特性の両方を同時に考慮する必要があると考えられる．

2．ゆらぎ成分

2）の「ゆらぎ成分」とは，心拍数変動や血圧変動に含まれる，ほぼ正弦波状の調和振動成分[12]や，いわゆる「1/fゆらぎ」のようなカオス的な成分[13][14]のことである．調和振動成分には主として2種類ある．ひとつは図3Aのような0.1Hz前後のMayer波と呼ばれる成分(LF成分)であり，もうひとつは図3Bのような0.3Hz前後の呼吸周波数に同期する成分である呼吸性洞性不整脈(HF成分)である．薬理学的な実験により，Mayer波は交感神経と副交感神経の状態を反映し，HF成分は副交感神経活動を反映することがわかっている[12]．(1)，(2)式のモデルに従う限り，呼吸性洞性不整脈や1/fゆらぎを表現することはできない

ただし，Mayer波が生じる原因だけは，このモデルに基づいて次のように説明できる可能性がある．すなわち一般に制御系の外乱抑制能力は感度関数$S(s)$

$$S(s)=\frac{1}{1-KC(s)G(s)} \quad \cdots\cdots (3)$$

で表される．ここでKはループ中に人為的に新たに加えたゲイン要素であり，システムのパラメータ変動を説明するためのものである．感度関数$S(s)$のゲインが小さいほど血圧に加わる外乱の影響が小さくなる性質がある．図4はKをパラメータとした時の$S(s)$のゲインを示したものであり，Kを大きくするほど低周波領域での$S(s)$のゲインが小さくなり，目標値への追従特性が良くなるが，逆に0.2Hz付

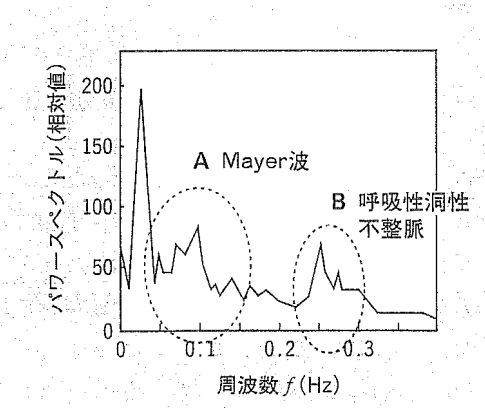

図3　ある健常者の心拍数のパワースペクトル

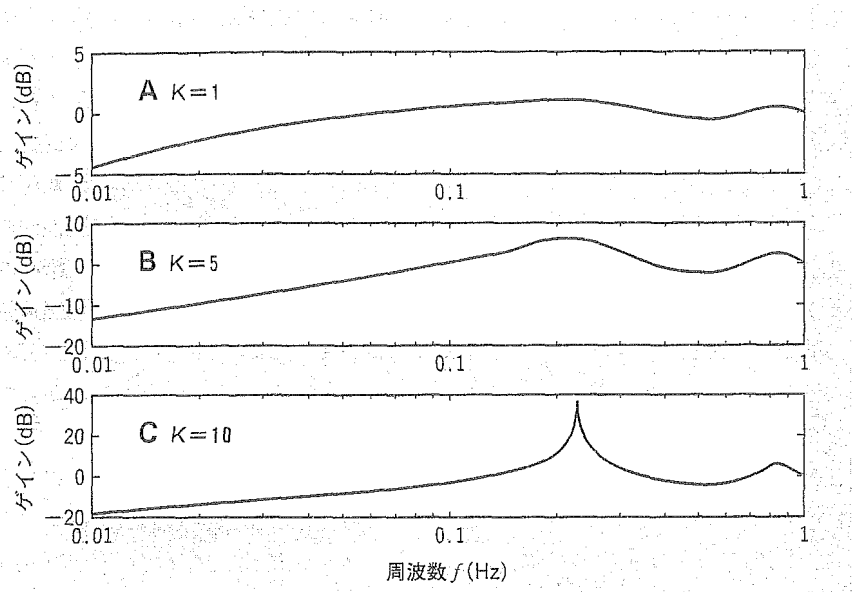

図4　図2の循環制御系の感度関数

近のピークが鋭くなる．このピークは，主としてむだ時間による位相遅れによって生じた調和振動成分の源であり，Mayer波を作り出す原因のひとつとして考えられる．これが血圧－心拍数間の閉ループ系の共振特性によって生起するという説[15]である．このような説以外に，Mayer波が血管運動を支配する中枢性の振動であるという説[16][17]や，それらを折衷した説[18]などがあるが，いまだ確定していない[18]．

図1Cは，図1Aにおける交感神経活動*SNA*の代わりに，非侵襲的計測が可能な心拍数*HR*を使った時の循環系のモデルである．ここで1回拍出量はほぼ不変と仮定している．n_{HR}とn_{BP}は外性信号であり，それぞれ，*HR*に含まれる*BP*由来でない成分，および*BP*に含まれる*HR*由来でない成分を表す．このようなモデルに2入力－2出力の2変数自己回帰(autoregressive moving average；AR)モデルを当てはめれば，閉ループ状態のまま非侵襲的に循環系をある程度同定することができる[19]．

しかし，通常はn_{HR}とn_{BP}に含まれる呼吸同期成分が強いため，2変数ARモデルを使っても同定しきれない部分が残る．そこでMullenら[20]は，インピーダンス法により瞬時肺容積*ILV*を計測し，*HR*，*BP*，*ILV*の3変数からなるモデルを考え，その同定を行って，自律神経をブロックした状態の機能変動とLF成分やHF成分の変化を表そうとしている．

また，Cavalcantiら[14]は，循環系のループ中にシグモイド状の非線形関数を仮定することによって，カオス的ふるまいが模擬できることを明らかにしている．

3．非定常性と非線形性

2-1．で述べた静特性の変動も，循環制御系が非定常(時変的)であることのひとつである．このほかの非定常な性質として，情動反応(情動性自律反応)がある．

情動反応は，外界からの刺激が有害か無害かなどの生物学的価値評価を脳が行った結果として生じる．たとえば，緊急反応(fight-or-flight response)[1]では，外敵に遭遇した時に戦うかあるいは逃げるための準備として，交感神経系や内分泌系が働き，筋肉への血流量の増加などを促進する．この時，血圧変動に関係なく心拍数が増大していくため，血圧変動と心拍数変動の関連性が一時的に低くなる．これは，図1Cのn_{HR}が*HR*に比して相対的に増加し，システムの線形性が低下することを意味する．

一方，起立，精神的緊張，心理的動揺，外部気温の急激な変動などが生じた場合には，特に末梢血管の収縮や拡張が生じる．これは血管抵抗の変動による血圧の変動をもたらす．このような血圧変動は心拍数の変動を直接反映しないため，図1Cのn_{BP}が*BP*に比して相対的に増加し，システムの線形性が低下することを意味する．

すなわち，安静時には血圧変動と心拍数変動の間に強い関連性があるのに対し，運動，心理的・精神的状態，外部環境の変化に応じてこの関連性が低下する．言い換えれば，図1Cの閉ル

ープ系のループの結合性が，薄くなったり元に戻ったりを常時繰り返している非定常なシステムが循環制御系である．

4．人工心臓の制御

自然心臓を切除して人工心臓に置き換える完全置換型人工心臓の場合，体液性調節および神経性調節の機能が存在しない．このため，流量制御のアルゴリズムを人為的に作らなければならない．しかし現在のところ，完全置換型人工心臓の体循環を司る左心側の拍出量制御法は，完全には確立されていない．なぜなら，生体が真に要求する心拍出量の目標値が未知であるからである．現在，有望と考えられている制御方式として，次の2つがある[21]．

A）スターリングの法則に基づいた制御

B）末梢血管抵抗に依存した制御

A)の制御は「1-1．のｉ)自己調節」で述べたスターリングの法則を利用するものである．すなわち，拍動型ポンプでは，ポンプ室に血液が完全に充満するまでを拡張期とし，充満した量を完全に排出するような制御を行うことにより，心房圧を直接計測せずに，スターリングの法則に近い特性を持つ流量制御が可能である．しかし，これまでの実験例によると，このような制御を行うと心拍出量が過剰になりやすく，中心静脈圧の上昇が抑えられないため，長期にわたる生存が困難であった[22]．この理由として，静脈から帰還する血液量を決める静脈還流量曲線は，生体によってその傾きやバイアスを変化させることができるのに対し，還流量に応じて拍出量を決めるための心機能曲線の形とその変化は人工心臓の特性で決まり，生体の方からは変えられないということが考えられている[23]．

B)の末梢血管抵抗に依存した制御は，いわゆる1/R制御法など[22)24)]のように，心拍出量を総末梢血管抵抗と大動脈圧の関数として決めようとするものである．この制御は，循環中枢自身が，自律神経系を介して操作することができる血管抵抗の情報に基づいて心拍出量を決定するような制御であり，動物実験での長期生存を達成している[25]．しかし，総末梢血管抵抗を得るには，大動脈圧・右心房圧・左心流量の計測が必要であり，実用化にはまだ難点が残っている．

末梢血管抵抗に依存した制御は，基本的に副交感神経の情報を利用していない．したがって，この制御の応答速度は遅く，すばやい情動反応も現れにくいと予想される．

3 情動反応の定量化

2-3．で述べたような循環系の非線形性や非定常性は，モデル化するには厄介な性質であるが，逆に，以下に示すように，情動反応の定量化，ひいては心理状態の把握のために積極的に利用できる可能性がある．

筆者ら[26)-30)]は，人間に視覚刺激などを与えた時の生体影響を定量化するための一手法として，Mayer波帯域に周波数成分を制限した血圧から心拍数までの相互相関係数$\rho(\tau)$(入出力信号の2乗平均値で規格化した相互相関関数)の最大値ρ_{max}を経時的に算出するという方法を提案した．これは，2-3．で述べたように，安静時には血圧変動と心拍数変動の間に強い関連性があるのに対し，何らかの心理的・精神的状態変化が起こった時にはこの関連性が低下するという性質を，ρ_{max}が反映する可能性があると予想されるからである．この様子を図5に示す．

実際のρ_{max}例は図6のようになる[26]．これは，ある健常被験者にジェットコースター搭載カメラからの実写立体映像を見せた時のデータである．ジェットコースター映像を選んだ理由は，この映像が恐怖心・興奮・動揺感・めまい・酔いなどの強い情動反応や生理的反応が顕著に誘発されると期待されたからである．この時，図6Aの安静時(映像提示なし)の拍内平均血圧*BP*と心拍数*HR*に符号を付けた-*HR*のMayer波は，*BP*に対しほぼ一定の位相遅れで-*HR*が追従する．心拍数*HR*に符号を付けたのは，位相を90度進めて表示上両者ができるだけ同相になるようにするためである．この場合，ρ_{max}は0.8ないし0.9程度となり，これを与えるτ_{max}は3ないし4秒である．このτ_{max}の値は(1)式の$C(j2\pi f)$にMayer波に対応する周波数$f=0.1$Hzを代入した時の位相遅れに近い値である．これに対し，図6Bの映像提示時では，*BP*と-*HR*の位相関係が乱れる部分が生じ，ρ_{max}は小さくなる．この場合，*BP*と-*HR*が同相に近い箇所があるため，τ_{max}は約2秒となった．

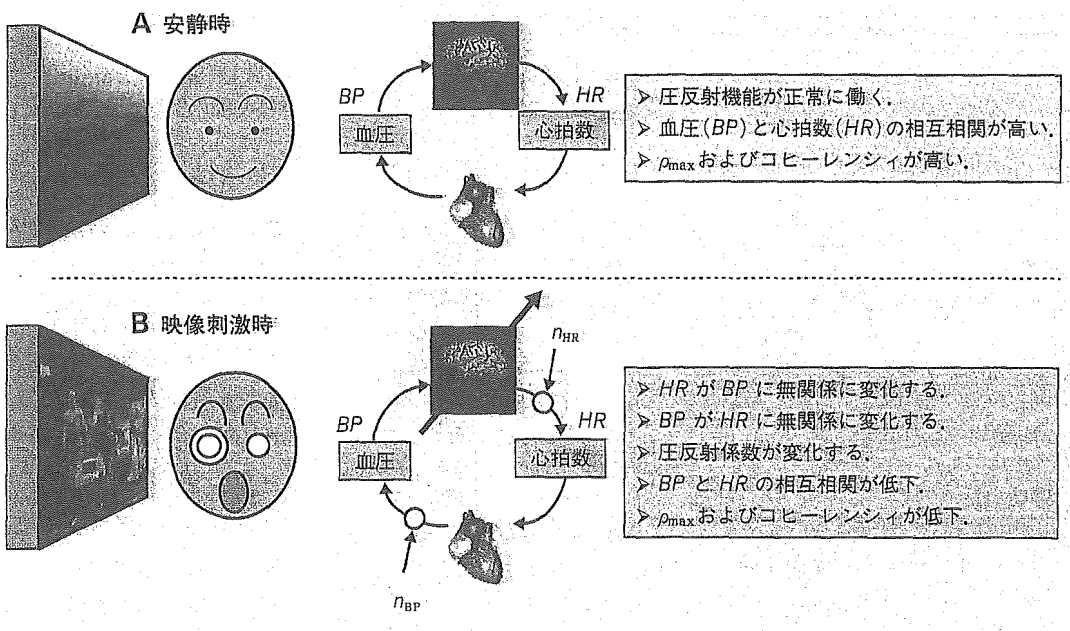

図 5　安静時と映像刺激時の圧反射系の相関性の相違
(文献 25 より引用)

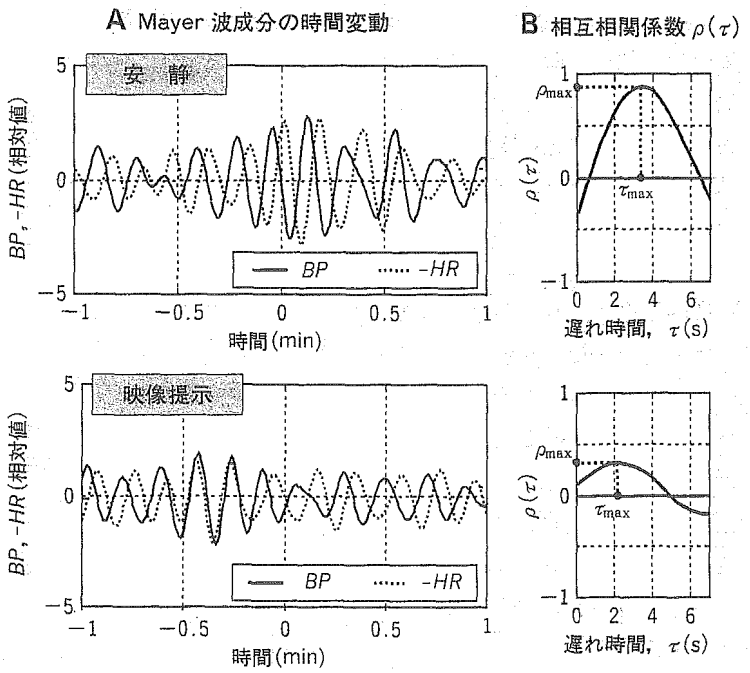

図 6　血圧(BP)および心拍数(-HR)の Mayer 波成分の時系列，および両者の相互相関係数 $\rho(\tau)$ とその最大値 ρ_{max}
(文献 26 より改変引用)

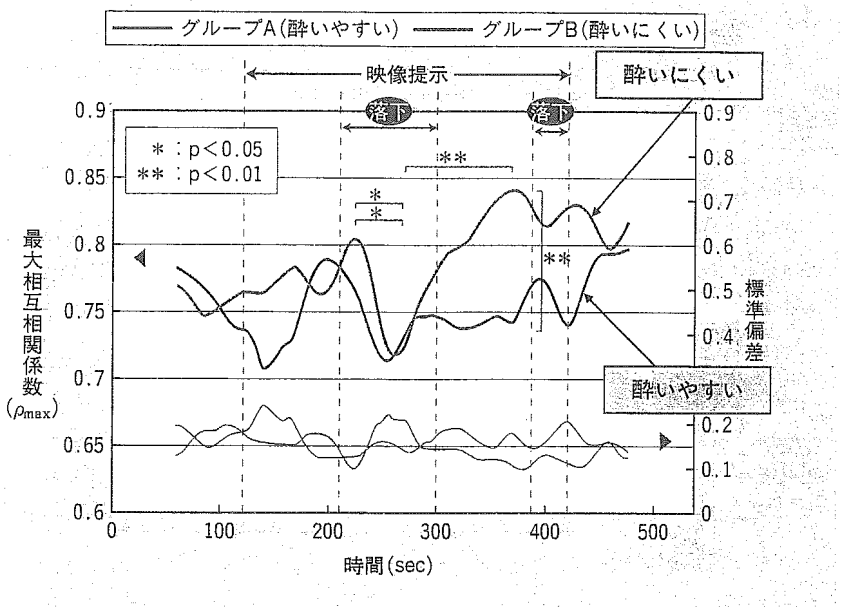

図7　ジェットコースター映像を提示した時のρ_{max}の推移

落下シーンの後，酔いやすい被験者(n＝18×2)より酔いにくい被験者(n＝15×2)のρ_{max}は，有意に速く回復した．
(文献26より引用)

図7は，図6と同様のジェットコースター映像を，乗り物酔いしやすい人18名と乗り物酔いしにくい人15名に提示する実験を行った結果である[26]．ただし，同一被験者に対し，内容が同じ2次元映像と立体映像の2種類を見せたため，データ数は2倍となっている．強い情動反応が生じていると思われる落下シーンでρ_{max}は急に下降し，落下終了後，酔いにくいグループのρ_{max}は上昇するにもかかわらず，酔いやすいグループでは有意に回復しなかった．ρ_{max}は情動反応に敏感に反応する指標であり，かつ，動揺病になりやすい体質(感受性)を反映するものであることが示唆された．ただし，図7の実験では試行時間が短いため，実際に動揺病の症状を訴えたのは4名程度であり，ρ_{max}が動揺病発症時の自律神経系の不調などをそのまま定量化するものではない．

ρ_{max}を求めるためには，拍数ごとの連続的な血圧計測が必要であり，これには大型で高価な装置が必要である．これに対し，血圧を計測する代わりに，血圧と逆相関する脈波伝播時間で置き換えることが考えられている[27]．脈波伝播時間は，安価なフォトセンサによる光電脈波で簡単に計測できるので，数多くの被験者を同時に対象とする実験が可能となる．このようにすると，新作映画などの人気の度合いなどを客観的に評価することが可能になるかもしれない．

おわりに

本稿では，自律神経系が支配する循環制御系は，その基本的動特性がかなり簡単な線形システムで近似できるにもかかわらず，心拍数や血圧の時系列としてのふるまいにゆらぎ成分を含み非線形性や非定常性も存在するなどの複雑な性質があることについて解説した．この性質の一部は，外敵の出現などで運動が予想される場面での準備行動に関係する．これは，神経－筋肉系などと比較して応答が遅い心臓血管系の動特性を補償する働きである．このような原始的な準備行動が進化していき，喜怒哀楽のようなさまざまな感情が体の反射的な変化，すなわち情動反応として表出するようになった可能性がある．

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Development of Detection Algorithm of Fatal Arrhythmia for a New Implantable Cardioverter Defibrillator

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Abstract— **This study discusses the validity of new methods of detecting fatal arrhythmia used for ICDs. The method utilizes the steady state gain of the system from the ECG signal to the ventricular volume signal. After analyzing the data measured in a dog, it has been shown that the system can be approximated by a second order resonant system. Moreover, it has been indicated that the batch-type least squares method with the short data window shifting every time the R-wave occurs is better rather than a few versions of recursive algorithms for identifying time-varying parameters.**

I. Introduction

Implantable cardioverter-defibrillators (ICDs) are effective therapeutic devices for rescuing patients with cardiac diseases from death caused by fatal arrhythmia such as ventricular fibrillation (VF) and ventricular tachycardia (VT). However, usual algorithms used in traditional ICDs for detecting VF and VT are based on information almost only on cardiac period, which makes it difficult to distinguish among normal heartbeat, VF, VT, and supraventricular arrhythmia[1].

On the other hand, we are developing a new ICD that can measure information on ventricular volume (VV) with an electrode driven by high frequency electric signal. The present report describes a new algorithm for detecting VF and VT, which is planed to introduce into our developing ICD, and discusses its validity and problems.

II. Methods

A. System Modeling and Identification of Steady State Gain K

As shown in Fig.1, consider a linear time-varying model with ECG signal as input and with VV signal as output. The model represents dynamic characteristic of the ventricle with different states: normal heartbeat and arrhythmia.

Suppose that the current heartbeat is normal. As shown in Fig.2, a R-wave of the ECG signal is similar to an impulse signal. After the R-wave comes, the contraction of the ventricle begins, and then VV decreases. Before the next R-wave comes, VV increases again due to the diastole of the ventricle. Thus, the input ($u(t)$) can be regarded as a series of impulses with a period of T and the output ($y(t)$) can be regarded as a sinusoidal wave with the same period.

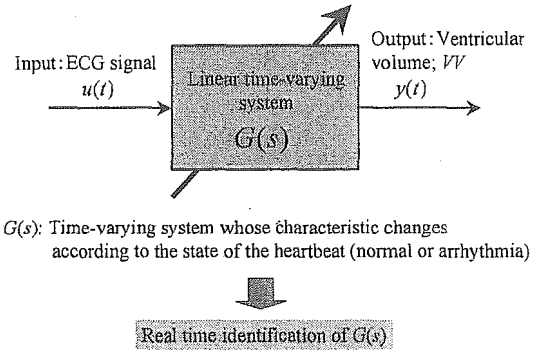

Fig.1 Linear time-varying system model from an input: ECG signal to an output: ventricular volume signal.

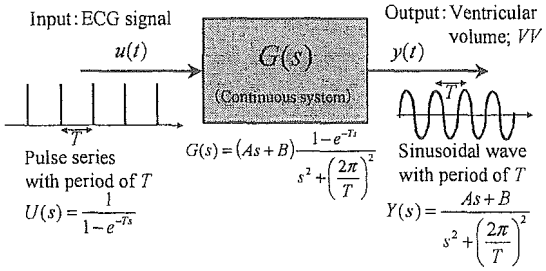

Fig.2 Transfer function $G(s)$ of the system.

The Laplace transform $U(s)$ of $u(t)$:

$$U(s) = \frac{1}{1-e^{-Ts}} \tag{1}$$

and the Laplace transform $Y(s)$ of $y(t)$:

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$$Y(s)=\frac{As+B}{s^2+\left(\frac{2\pi}{T}\right)^2} \tag{2}$$

yield the transfer function $G(s)$ of the system:

$$G(s)=(As+B)\frac{1-e^{-Ts}}{s^2+\left(\frac{2\pi}{T}\right)^2} \tag{3}$$

where A and B are, for a short time, constants depending on the phase shift and the amplitude of $y(t)$. Equation (3) means that the system is a second order resonant system with natural frequency of T^{-1} [Hz].

If the heartbeat changes into VF or VT, the parameters A, B, and T will changes drastically. By estimating these parameters, it is possible to recognize the state of the heartbeat. In place of the above continuous-time model, an ARX model (autoregressive model with exogenous input) is introduced for easy identification.

Let the input $u(t)$ and the output $y(t)$ be sampled every Δt [s] to be $u(k)$ and $y(k)$, respectively. The ARX model is represented by

$$\begin{aligned} y(k)=&a_1y(k-1)+a_2y(k-2)+\cdots+a_ny(k-n)\\ &+b_1u(k-d)+b_2u(k-1-d)\\ &+\cdots+b_mu(k-m+1-d)+w(k) \end{aligned} \tag{4}$$

where $d\geq 1$ is a time delay and $w(k)$ is residue assumed as white noise. Pulse transfer function $G(z)$ from $u(k)$ to $y(k)$ is

$$G(z)=\frac{\left(b_1+b_2z^{-1}+\cdots+b_mz^{-m}\right)z^{-d}}{1-\left(a_1z^{-1}+a_2z^{-2}+\cdots+a_nz^{-n}\right)} \tag{5}$$

The parameters included in (4) can be identified in a real time fashion by a few types of least squares (LS) methods to cope with time-varying characteristic.

In the present study, we regard the steady state gain K as a simple index to represent the state of the heartbeat. The steady state gain K is defined as the ratio of $y(\infty)$ to $u(\infty)$ when $k\rightarrow\infty$ and calculated from

$$K=\frac{y(\infty)}{u(\infty)}=\frac{b_1+b_2+\cdots+b_m}{1-(a_1+a_2+\cdots+a_n)} \tag{6}$$

by letting $z\rightarrow 1$ in (5).

On the other hand, if the heartbeat is in VF, the input, i.e., the ECG signal will be irregular in amplitude and period, and the output, i.e., the amplitude of *VV* signal will be almost zero. In this case, the steady state gain K will be reduced from that in the normal heartbeat.

If the continuous-time system can be approximated by (3), the corresponding simplest discrete-time system (4) will have order of $n=2$ and $m=1$. The phase characteristic of the system will be able to be adjusted by the time delay d.

B. Several Versions of Identification Methods

1) Batch-type least squares method

To ascertain the validity of the model (3), the batch-type least squares (LS) method (off-line LS method) was applied to the data obtained in the normal heartbeat. First, the ECG signal and *VV* signal were, respectively, measured in a dog with an ECG sensor inserted into the right ventricle and a conductance catheter inserted into the left ventricle. These signals were filtered through a band-pass filter with the pass-band of 0.5Hz-3Hz The batch-type least squares method was applied to 25s-long data obtained in the normal heartbeat. The orders of the system was $n=2$ and $m=1$. The time delay d was chosen so that the loss function can be maximized.

2) Recursive least squares method with forgetting factor

The recursive least squares (RLS) method with the forgetting factor λ [2] was used to estimate the time-varying parameters. It is known that if λ is chosen to be small to pursuit the change in parameters, the estimates tend to be unstable.

3) Constant trace algorithm

The constant trace algorithm [2] is known as a method that can compensate for the defect of RLS method with the forgetting factor. The algorithm works so that the trace of the matrix gain can remain constant by automatically changing the forgetting factor. However, how to chose the desired value of the trace has a trade-off between stability and speed of the estimation.

4) Batch-type LS method with data window shifting continuously

In general, recursive-type identification algorithms have parameters that should be adjusted to track the time-varying parameters of the system to be identified. However, such adjustment must consider the trade-off mentioned above. To cope with such a problem, we used a batch-type LS method that shifts a short (a few second-long) data window continuously.

5) Batch-type LS method with data window shifting every time R-wave occurs

The batch-type LS method with data window shifting continuously consumes much computational time and yields periodical fluctuation caused by the result of identification that changes depending on the beginning time of the data window. To avoid these problems, we used a batch-type LS method with a short data window that shifts every time the R-wave occurs. It is expected that this method will reduce its computational time and have no fluctuation in the estimates.

III. RESULTS

A. Batch-Type Least Squares Method

Fig.3 shows measured the left ventricular volume (*LVV*) signal and ECG signal in the normal heartbeat. The estimated *VV* obtained from the batch-type least squares method is depicted by the broken line. In this case, the time delay d was determined as $d = 27$ (270ms). The estimated volume waveform agrees well with the measured one except the parts of local extrema.

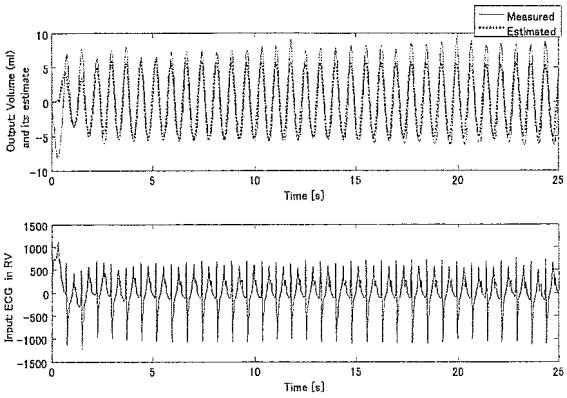

Fig.3 Result of identification using 25s-long data obtained from a dog. Top: measured (solid line) and estimated (broken line) *VV* signal as output. Bottom: Measured ECG signal as input.

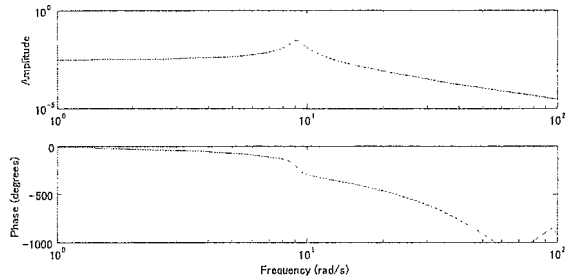

Fig.4 Bode diagram corresponding to Fig.3.

Fig.4 shows the Bode diagram corresponding to the system identified with the data of Fig.3 on the basis of the ARX model (4) letting $n = 2$, $m = 1$, and $d = 27$. The gain characteristic of this figure has a resonant peak at about 9rad/s (1.5Hz), and then this figure indicates that the system from the ECG signal to *VV* can actually be approximated as the second order resonant system expressed in (3).

B. Recursive Least Squares Method with Forgetting Factor

Fig.5 shows a) ECG signal in the right ventricle, b) *LVV*, c) steady state gain K calculated by (6), and d) the trace of the gain matrix $P(k)$ in VT. The RLS method with the forgetting factor $\lambda = 0.97$ was used to estimate the parameters included in (4) on the basis of the data obtained in the same dog. In this case, the time delay was $d = 20$ (200ms) minimizing the loss function during the normal heartbeats. As shown in Fig.5e), rapid increase in K can be found but its wave form is oscillatory. On the contrary, when λ was increased to get more stable results, K increased much more slowly. Moreover, K is noisy during VT. This corresponds to increase in the trace of $P(k)$.

C. Constant Trace Algorithm

On the basis of the same data as Fig.5, Fig.6 shows the result obtained from the constant trace algorithm used so that the trace of $P(k)$ may be constant. In this case, the set point of the trace was 0.3. As shown in Fig.6e), rapid increase in K can be found but its waveform is oscillatory in the same way as Fig.5. However, the behavior of K is stable, which would be caused by the suppressed trace. It has already been ascertained that when the set point of the trace was reduced from 0.3, the response of K became slower.

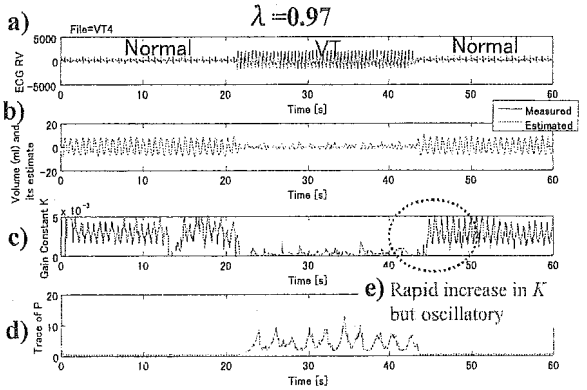

Fig.5 Result from the RLS method with the forgetting factor $\lambda = 0.97$ in VT. a) ECG signal in the right ventricle, b) *LVV*, c) steady state gain K calculated by (6), and d) the trace of the gain matrix $P(k)$.

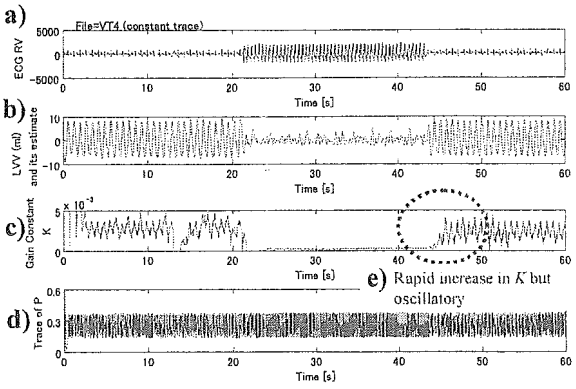

Fig.6 Result from the constant trace algorithm in RLS method for the same data as Fig.5 (VT). a) ECG in RV, b) *LVV*, c) K, and d) the trace of $P(k)$. The set point of the trace was 0.3.

D. Batch-type LS method with data window shifting continuously

Fig.7 shows the result obtained from the batch-type LS method that shifts an 1s-long data window continuously. Descending and ascending speeds in K are similar to those of Fig.5 as shown in Fig.7e). However, it seems that stability of K has improved.

E. Batch-type LS method with data window shifting every time R-wave occurs

Fig.8 shows the result obtained from the batch-type LS method that shifts the 1s-long data window every time the R-wave occurs. As expected, the fluctuation in K during each cardiac period found in Fig.7c) was eliminated, and then the time series of K was obtained beat by beat as shown in Fig.8c). It can be seen that the time series of K is stable in the normal heartbeat except the extrasystole found at $t = 14$ s.

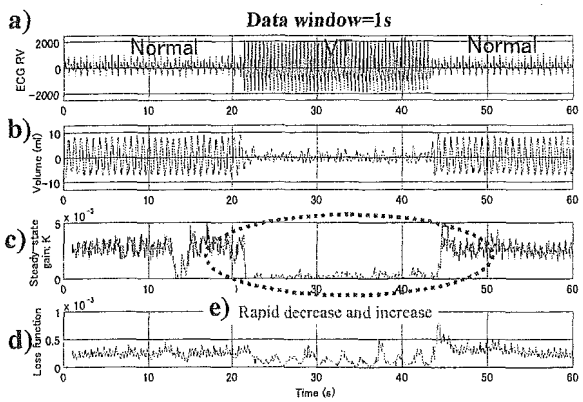

Fig.7 Result from the batch-type LS with the data window shifting continuously for the same data as Fig.5 (VT). a) ECG in RV, b) *LVV*, c) K, and d) Loss function.

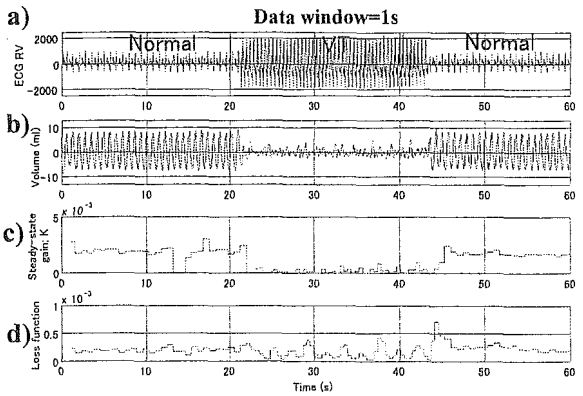

Fig.8 Result from the batch-type LS with the data window shifting every time R-wave occurs for the same data as Fig.5 (VT). a) ECG in RV, b) *LVV*, c) K, and d) Loss function.

IV. Discussion

The advantage of the methods estimating the steady state gain K is that the value of K would provide information on the efficiency of ventricular contractility or the state of normal heartbeat in terms of system identification. Unlike in the case of traditional methods for ICDs depending only on the ECG signal, the methods using K determined from both the ECG and the *VV* signals are possible to give richer information on the system and lead to automatic detection of fatal arrhythmia.

However, recursive identification algorithms have a problem of the trade-off between estimation speed and stability, which has been ascertained here (Figs.5 and 6).

On the other hand, the batch-type LS methods with the shifting data window could give more stable and rapid estimation as shown in Fig.7. The length of the data window should be minimized because the length determines the estimation speed. It is, however, clear that the length cannot become shorter than the cardiac period (~1s)

The method using the data window that shifts every time the R-wave occurs is more stable and can save computational time. However, this method must recognize the R-wave accurately.

In the present study, we concentrated only on K. To distinguish among normal heartbeat, VF, VT, and supraventricular arrhythmia, we should use not only information on the position of poles but also low frequency components that were eliminated through the band-pass filter.

V. Conclusion

This study has discussed the validity of new methods of detecting fatal arrhythmia used for ICDs. The method utilizes the steady state gain of the system from the ECG signal to the ventricular volume signal. After analyzing the data measured in a dog, it has been shown that the system can be approximated by a second order resonant system. Moreover, it has been indicated that the batch-type LS method with the short data window shifting every time the R-wave occurs is better rather than a few versions of recursive algorithms for identifying time-varying parameters.

In further studies, we should improve the proposed methods so as to distinguish among normal heartbeat, VF, and VT, using other information, for example, the position of poles.

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Central Sympathetic Inhibition Augments Sleep-Related Ultradian Rhythm of Parasympathetic Tone in Patients With Chronic Heart Failure

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