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An Experimental Study on Automatic Control of Mean Arterial Pressure in Hypertensive Rabbits by means of Adaptive Control System using Sodium Nitroprusside Dihydrate

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= Abstract =There are clinical conditions when rapid control of hypertension is needed, such as malignant hypertension, hypertensive left ventricular failure and encephalopathy, and perioperative management of hypertensive patients requiring emergency operation.

The rapid reduction of blood pressure can be achieved with closed-loop type blood pressure controllers safely and rapidly. Among them, pole assignment self-tuning control algorithm, a newly adopted adaptive control algorithm using sodium nitroprusside dihydrate, showed excellent results in our experiment with hypertensive rabbits. Convergence time to a set point was less than 630 seconds and standard deviation of maintained blood pressure was within 3.9 mmHg.

Key Words: ***Hypertension, On-line parameter estimation, Blood pressure controller, Adaptive control algorithm, Sodium nitroprusside dihydrate***

INTRODUCTION

There are some clinical conditions when rapid reduction of blood pressure is critical for life-saving. These include malignant hypertension, eclampsia with hypertensive encephalopathy, intracranial hemorrhage, hypertensive left ventricular failure with pulmonary edema and afterload reduction after open heart surgery. Perioperative management of hypertensive patient requiring emergency operation is also included (Beeson *et al.* 1979; Lee 1979).

Generally, continuous intravenous infusion of the drugs having rapid onset and short action is effective for these conditions. However, hypotensive collapse is a complication which requires continuous blood pressure monitoring in intensive care unit.

To reduce that risk and for convenience, closed-loop type blood pressure controller, which automatically calculates an adequate drug amount and infuses it according to previous responses, has been developed. These controllers are

1) Proportional-integral-differential gain controller (Sheppard and Sayers 1977)
2) Optimal feedback controller (Koivo *et al.* 1978)
3) Adaptive controller (Arnsparger *et al.* 1983)

In our experiments using adaptive controller, it was shown that this system could control blood pressure effectively and safely.

CONTROL ALGORITHMS AND MODELING

I. Characteristics of physiological system

In physiological system, blood circulation and metabolism of various substances in body can usually vary according to changes in external and/or internal environment. Moreover, control of blood pressure is regulated by many factors such as nervous system, cardiac output and endocrine system, *etc.*

Therefore, the pharmacodynamics between infu-

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sion rate of hypotensive drugs and mean arterial pressure may exhibit following characteristics;

1. slowly time varying parameters
2. unknown, possibly variable time delay
3. nonminimum phase behavior (which causes feedback controller to be unstable)
4. constraints on output response rate and magnitude of input
5. nonlinear system inherently
6. stochastic variables

It is desirable that blood pressure controller is designed after considering the above difficulties sufficiently. Above all, it is necessary that its algorithm should ensure the stability of the overall system. In following sections, two control algorithms are summarized; one is a pole assignment self-tuning control system, which we used as a new method, the other is an one-step ahead minimum variance controller used by Arnsparger *et al.* (1983).

II. Pole assignment self-tuning control (PASTC)

This algorithm has been developed by Wellstead *et al.* 1979 & 1981). Although PASTC is not an optimal control method, it is more robust for stability and can be applied with more ease to the nonminimum phase and unknown time delay system. Thus this method can be useful to control blood pressure.

Assuming that the maximum delay factor, k (which will be defined in section IV) is equal to 2, the relationship between mean arterial pressure and infusion rate of hypotensive drug can be described with the second order autoregressive moving average (ARMA) model.

$$y(t)+a_1(t)y(t-1)+a_2(t)y(t-2)=b_1(t)u(t-1)+b_2(t)u(t-2)+b_3(t)u(t-3)+b_4(t)u(t-4)+e(t)+c_1(t)e(t-1)+c_2(t)e(t-2)+d \quad (1)$$

where, the variables y(t), u(t) and e(t) are sequences of points at the integral time steps (t= 0,1,2,..) which represent uniformly sampled versions of system output (mean arterial pressure), control input (drug infusion rate) and model fitting error which generates unobservable disturbances, respectively. $a_i(t)$, $b_i(t)$ and $c_i(t)$ are parameters of the model which vary according to differences in subject or operation time course, and "d" is an initial pressure level. During operation of the pressure control, the parameters are estimated at every sampling time by a recursive least square estimator (RLSE) to adopt any variation resulted from the change of physiologic factors. With these estimated parameters (a_i, b_i, c_i, d) and input-output data, a new input that will be infused till the next sampling time is calculated by the following equations;

$$u(t)=-g_0(t)y(t)-g_1(t)y(t-1)-f_1(t)u(t-1)-f_2(t)u(t-2)-f_3(t)u(t-3)+h(t)y^*-m(t)d \quad (2)$$

$$h(t)=\frac{1+t_1+t_2}{b_1+b_2+b_3+b_4},$$

$$m(t)=\frac{1+f_1+f_2+f_3}{b_1+b_2+b_3+b_4} \quad (3)$$

where, $g_i(t)$ and $f_i(t)$ are control parameters and y^* is a set point.

The controller in PASTC is chosen in such a way that the closed-loop poles are placed at prespecified positions [$T(z^{-1})=1+t_1z^{-1}+t_2z^{-2}$], where z^{-1} is represented as the backward shift operator. The polynomial $T(z^{-1})$ is preselected by the designer with consideration of the required response rate. The control parameters, $g_i(t)$ and $f_i(t)$ are obtained from the following diophantine equation derived from equation (1) and (2).

$$\begin{bmatrix} 1 & 0 & 0 & b_1 & 0 \\ a_1 & 1 & 0 & b_2 & b_1 \\ a_2 & a_1 & 1 & b_3 & b_2 \\ 0 & a_2 & a_1 & b_4 & b_3 \\ 0 & 0 & a_2 & 0 & b_4 \end{bmatrix} \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ g_0 \\ g_1 \end{bmatrix} = \begin{bmatrix} t_1-a_1 \\ t_2-a_2 \\ 0 \\ 0 \\ 0 \end{bmatrix} \quad (4)$$

The flow of this algorithm can be summarized as follows.

1) The initial data [t_i, u(o), y(o)] are given.
2) Update output y(·).
3) Estimate the parameters of model by RLSE.
4) Calculate the control parameters from equation (4).
5) Calculate a new control input from equation (3).
6) The steps 2), 3), 4) and 5) are repeated at each sampling interval.

A block diagram of PASTC is shown in Fig. 1.

This approach has several advantages over other self-tuning models. The problem of delay of response can be neglected by extending the degree of numerator parameters by the maximum time delay likely to be encountered. In other words, although the exact delay in response of the subject is unknown and possibly variable, this restricted condition can be treated by assuming only the maximum time delay. Moreover, since the aim in PASTC is to manipulate the closed-loop poles to pre-assigned positions which ensure a high system

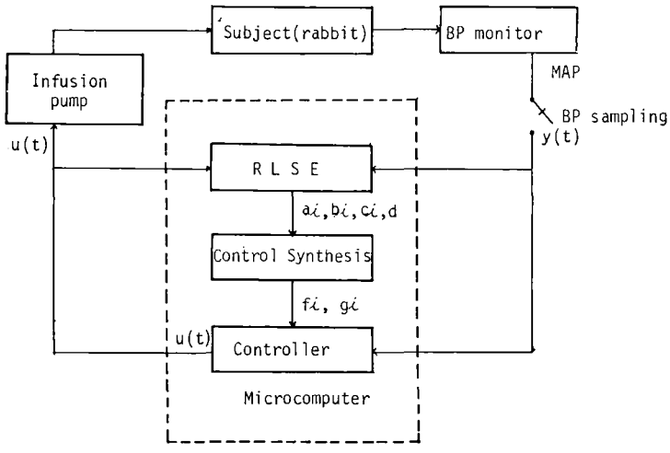


Fig. 1. Schematic diagram of pole assignment self-tuning algorithm. MAP; mean arterial pressure, BP; blood pressure. RLSE; recursive least square estimator, a_i, b_i, c_i, d, f_i, g_i; parameters. y(t); output, samled blood pressure on time "t". u(t); input, calculated drug infusion rate on time "t".

stability, this approach is a favoured method to avoid nonminimum phase behavior which causes inverse unstable mode. However, if a system is a nonminimum phase or the exact delay is unknown, general optimal self-tuning controls will lose control, and probably go unstable (Aström and Wittenmark 1973).

III. One-step ahead minimum variance control algorithm

This algorithm developed by Goodwin and Sin (1984) is based on RLSE and one-step ahead control law with a prior knowledge of the exact time delay. One-step ahead controller has the advantage of minimizing both the rates of changes of input and output tracking error, that is, it is obtained such that a control law will minimize the following cost function;

$$J(t+1)=E\{\frac{1}{2}[y(t+1)-y^*(t+1)]^2+\frac{\lambda}{2}[u(t)-u(t-1)]^2\} \quad (5)$$

where, "λ" is a weighting factor.

Arnsparger *et al.* (1983) represented a system model for mean arterial pressure control as the second order ARMA process with assuming maximum delay factor, k=1.

$$y(t)+a_1y(t-1)+a_2y(t-2)=b_0u(t-1)+b_1u(t-2)+b_2u(t-3)+e(t)+c_1e(t-1)+c_2e(t-2)+d \quad (6)$$

where, assumed that $b_0=0$.

The one-step ahead predictor using pseudo-linear regression technique for this model is;

$$\hat{y}_0(t+1)=\alpha_1y(t)+\alpha_2y(t-1)+\beta_0u(t)+\beta_1u(t-1)+\beta_2u(t-2)-c_1\hat{y}_0(t)-c_2\hat{y}_0(t-1)+d \quad (7)$$

The performance measure is minimized by the following one-step ahead control law;

$$u(t)=\frac{-1}{\beta_0^2+\lambda}[\beta_0\{\alpha_1y(t)+\alpha_2y(t-1)+\beta_1u(t-1)+\beta_2u(t-2)-y^*+d-c_1\hat{y}_0(t)-c_2\hat{y}_0(t-1)\}-\lambda u(t-1)] \quad (8)$$

The flow of this approach can be summarized as follows.

1) The initial data [$\alpha_i(o)$, $\beta_i(o)$, $c_i(o)$, y(o), $\hat{y}$(o), u(o), d] are given
2) Update output y(·).
3) Estimate the parameters of predictor by RLSE.
4) Calculate new control law from equation (8).
5) The steps 2), 3) and 4) are repeated at each sampling interval.

Since it is assumed that the delay time is equal to the sampling period in this algorithm, it is necessary to know the exact delay time. When the delay time is not integer multiple of a sample interval, and if "λ" is not chosen properly, the system will go unstable (Goodwin and Sin 1984; Wellstead and

Table 1. The time delay of hypotensive drugs

Patient	Agent	Dose (μg/kg/min)	Delay (min)	Time to minimum (min)	Time to Recovery (min)
1	Trimethaphan	9.0	0.6	2.7	3.8
2	〃	8.2	0.4	2.2	4.2
3	〃	12	0.8	4.0	6.0
4	〃	6	0.5	3.3	4.2
5	〃	17.4	0.6	2.8	6.6
6	Sodium nitroprusside	5.7	0.6	1.9	3.5

Sanoff 1981). Therefore, mean arterial pressure control using this approach is difficult to ensure a high stability because of unknown and variable time delays. This problem has been shown by our experimental models.

IV. Determination of sampling time

A time that takes from a drug infusion to an onset of pressure response is defined as a system time delay. Sheppard *et al.* (1977) have reported that with rapid onset hypotensive drugs mean arterial pressure began to decrease after a delay, corresponding to one circulation time (20 to 45 sec.), which took at a minimum 1.2 to 1.9 minutes, and that delay depended on the subject and time course (Table 1).

A sampling time for digital control can be chosen by the following equation (Kurz and Goedecke 1981).

$$\frac{1}{15}T_{95}<T_0<\frac{1}{4}T_{95} \qquad (9)$$

Where, T_0 is a sampling time and T_{95} is a 95% settling time of a transient function. That is the time necessary to reach a minimum pressure level in Table 1. We choose $T_0=30$ sec. from Table 1 and equation (9). Assuming that a maximum time delay, TDmax. is 60 seconds, then the delay factor, k becomes $2(k=TDmax./T_0)$.

MATERIALS AND METHODS

White rabbits, weighing 2.1 to 2.5 kg, were used as experimental models. Blood pressure was monitored from the cannulated carotid artery by blood pressure monitor, ICH-5H polygraph. Analog-digital converter sampled blood pressure at each sampling time and delivered it to a microcomputer, Apple II. The microcomputer calculated an adequate drug amount according to the programmed algorithm and ordered infusion pump, IMED 922 to deliver the hypotensive drug to animal at a given infusion rate (Fig. 2).

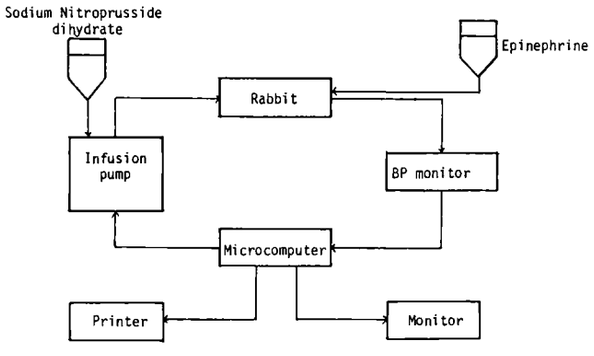


Fig. 2. Diagram of adaptive blood pressure control system.

Diluted sodium nitroprusside dihydrate (100 and 200 μg/ml, in 5% dextrose water) was used as a hypotensive agent. Hypertension was induced by unilateral renal artery ligation (Goldblatt kidney), unilateral carotid artery ligation or continuous infusion of diluted epinephrine solution.

RESULTS

Normal mean arterial pressure of rabbit is regarded as 100 to 110 mmHg. It was chosen as 100 or 110 mmHg arbitrarily in our experiments. The initial pressure was between 122 and 163 mmHg.

13 experiments were performed, and 3 cases of them with one-step ahead minimum variance control system were not controllable and were excluded from our study. Among remained 10 experiments, 8 involved PASTC system (Exp. 1 to 8) and 2 cases involved one-step ahead minimum variance control system (Exp. 9 and 10). The results were excellent in maintaining the desired blood pressure except in Experiment 9. The convergence time for reaching desired pressure level($\pm$10 mmHg) was laid between 300 and 630 seconds, and standard deviation of the maintained pressure was less than 3.9 mmHg. In experiment 9, blood pressure was maintained but at 7.8 mmHg below the desired value and convergence time was prolonged to 21 minutes. The sampling time was chosen as 30 seconds in PASTC system (Exp. 1 to 8), and in 3 cases excluded, 20 seconds, in Experiment 9, 45 seconds and 60 seconds in Experiment 10 with one-step ahead minimum variance control system. The excellent result of Experiment 10 could be obtained probably because sampling time was near to the time delay (Table 2, Fig. 3-12).

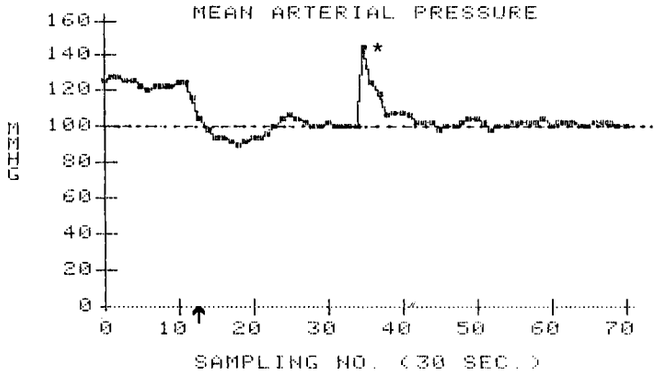
In Experiment 1, 6 and 8, blood pressure rapidly rose due to rabbits' excitement during procedure, but in a following few minutes it was maintained at the previous level (Fig. 3, 8 and 10).

In Experiment 8, hypotensive drug was used in double concentration (200 μg/ml) and subtle changes of infusion rate caused instability of the maintained pressure.

DISCUSSION

Automated drug administration system to regulate mean arterial pressure has been presented for rabbits. Our approach was directed to prompt

Exp. 1



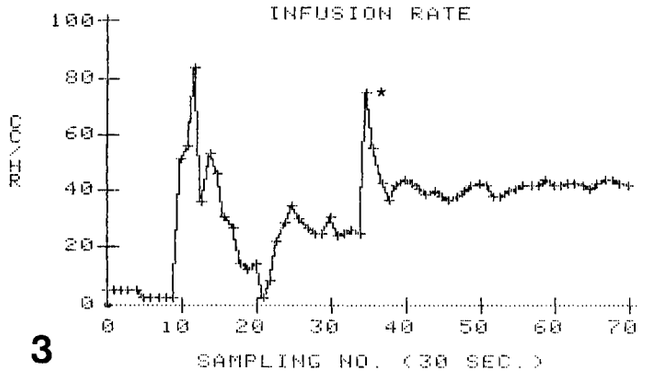


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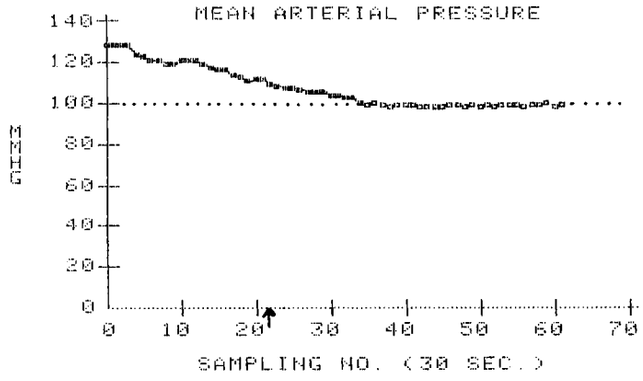
Fig. 3

Exp. 2



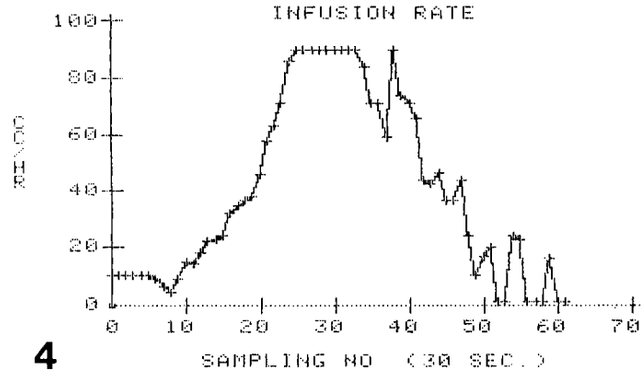


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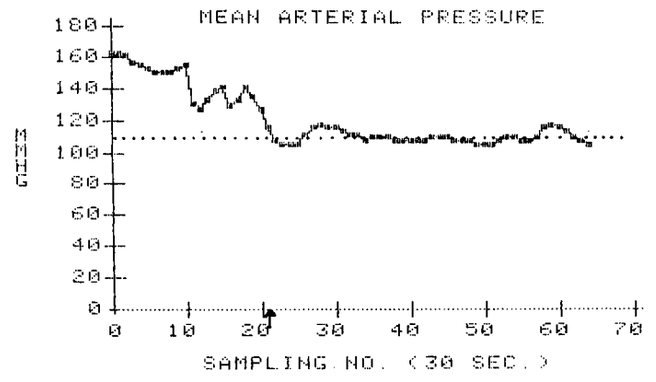
Fig. 4

Exp. 3



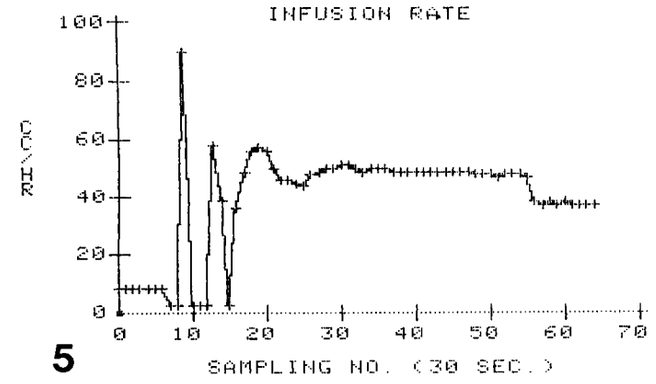


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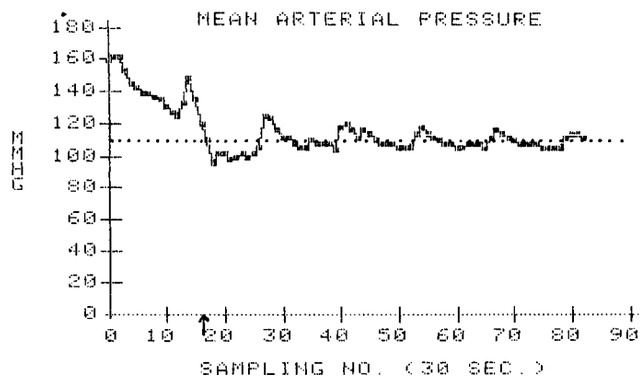
Fig. 5

Exp. 4



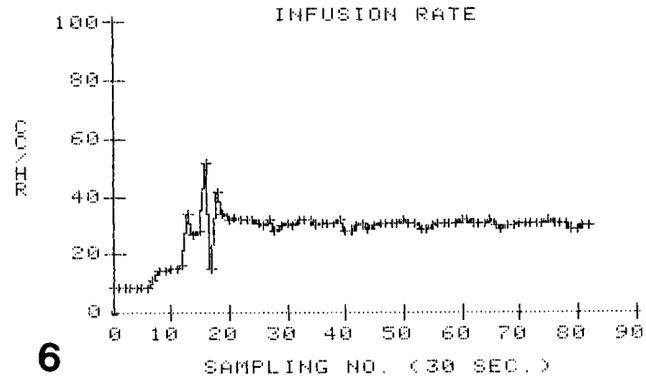


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Fig. 6

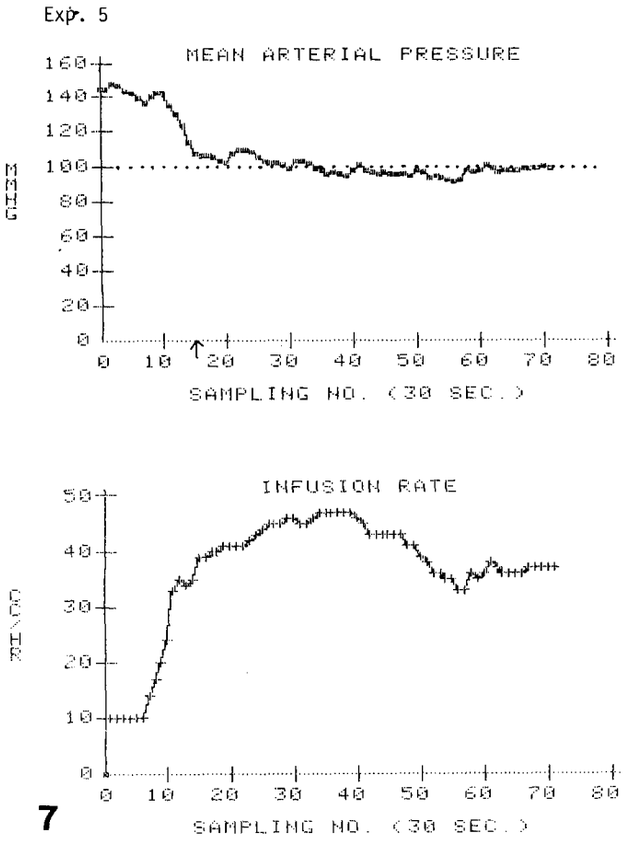

Fig. 7

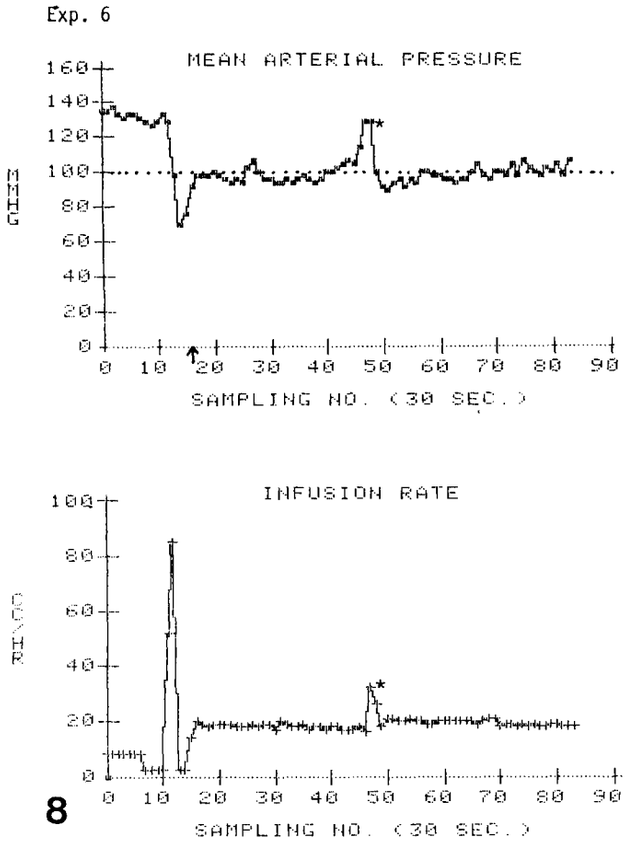

Fig. 8

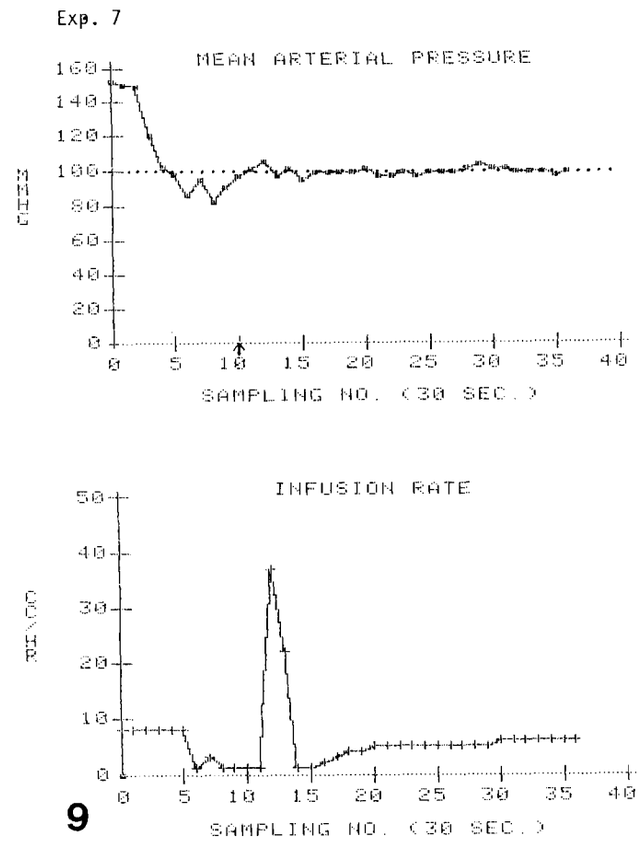

Fig. 9

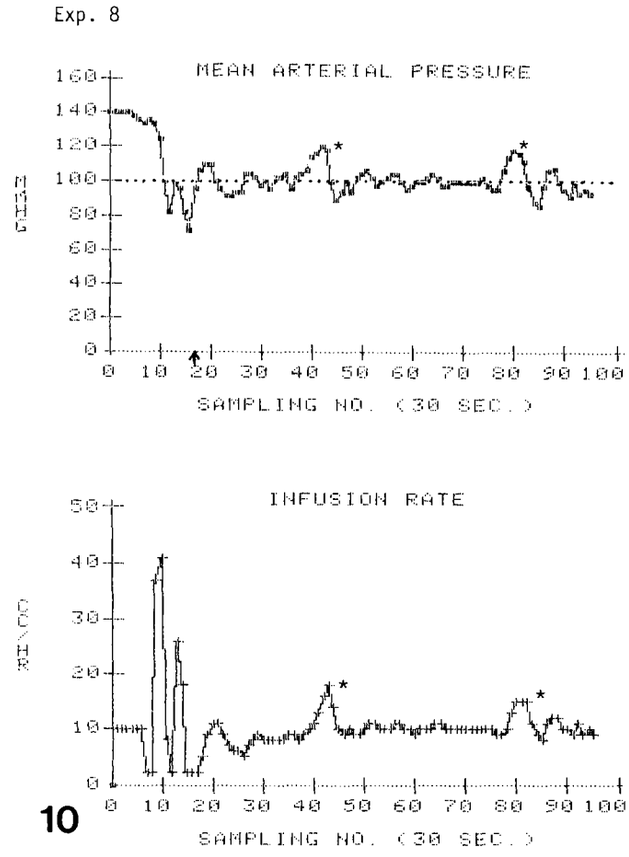

Fig. 10

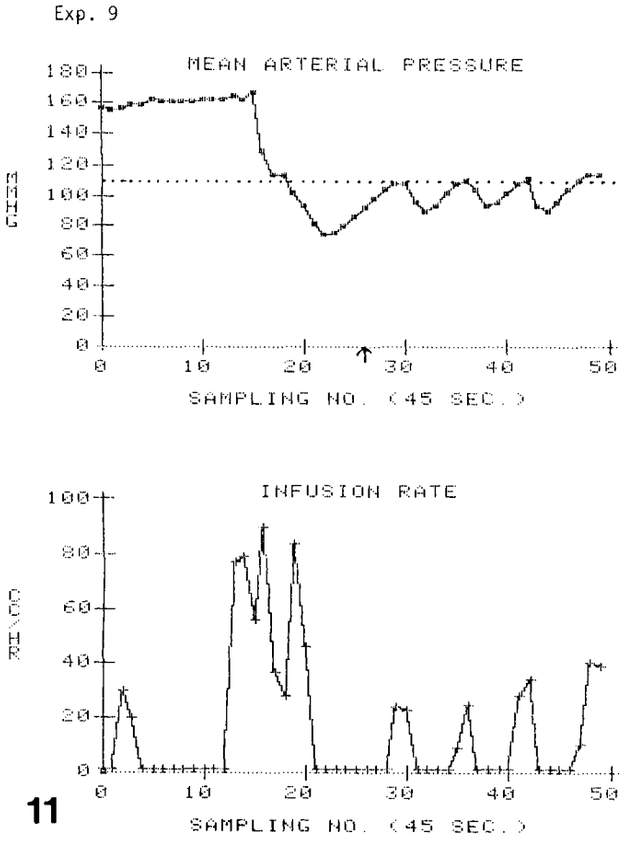

Fig. 11

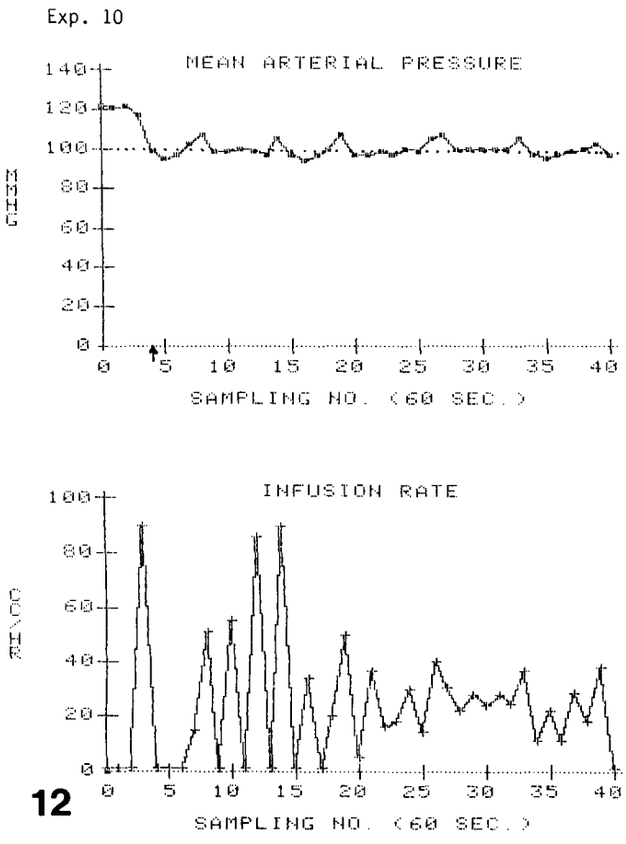

Fig. 12

Fig. 3. to Fig. 10. Changes of mean arterial pressure and corresponding infusion rate of sodium nitroprusside dihydrate in hypertensive rabbit, by pole assignment self-tuning control. dotted line; a set point (desired pressure level), ↑; convergence time, *; rabbit's excitement

Fig. 11 & Fig. 12. Changes of mean arterial pressure and corresponding infusion rate of sodium nitroprusside dihydrate in hypertensive rabbit, by one-step ahead minimum variance control. dotted line; a set point (desired pressure level), ↑; convergence time.

Table 2. The maintained mean arterial pressure and convergence time of each experimental model

Experiment No.	Applied Algorithm	Initial MAP(mmHg)	Set point (mmHg)	Sampling Time(sec.)	Convergence Time(sec.)	Maintained MAP±SD
1	PA	126	100	30	390	101 ±1.9
2	PA	128	100	30	630	99.7±2.1
3	PA	163	110	30	630	110 ±3.5
4	PA	159	110	30	480	110 ±3.8
5	PA	145	100	30	420	98.1±2.9
6	PA	135	100	30	480	97.5±3.9
7	PA	152	100	30	300	99.2±2.1
8	PA	140	100	30	510	100.3±3.5
9	MV	157	110	45	1,260	102.3±7.7
10	MV	122	100	60	240	99.8±3.4

MAP: mean arterial pressure, SD: standard deviation, PA: pole assignment self-tuning control, MV: one-step ahead minimum variance control.

control of blood pressure in hypertensive crisis and in patients undergoing surgery. Different types of external controller are used to maintain a desired value of mean arterial pressure. A classical PID controller is designed on the basis of a first-order transfer function and extensive prior testing for the purpose of tuning the three factors (P, I, D) (Sheppard 1980). This method is also mainly based on engineering judgement to adjust the gain of a controller because of variable parameters and delays.

An optimal feedback controller by Koivo *et al.* (1978 & 1981) is a type of minimum variance control on the basis of a linear first-order differential model with constant parameters. But since parameters are not time invariant and the model is approximated as the first-order differential equation, we think that this approach has difficulty to ensure a stable pressure control for the overall physiological systems. An open-loop test is also required for identifying coefficients preliminarily.

The adaptive control method is based on an on-line parameters estimator and input-output model. Since this method will adjust model coefficients to adapt to mean arterial pressure response characteristic of a particular subject, extensive preliminary testing is not necessary. As with the previous explanation, if a delay of a given subject is not equal to a sample period, a minimum variance type of self-tuning controller used by Arnsparger *et al.* (1983) cannot ensure the stability. That paper did not show evidence on satisfactory operations of various subjects.

Our experimental results using Arnsparger's approach, only one out of five cases, which was regarded as satisfying $k=1$ occasionally, provided satisfactory features (Table 2, Fig. 12). Our approach using PASTC (Wellstead *et al.* 1979) with choice of $K=2$ and $T_0=30$ sec. has shown very satisfactory results in all the eight cases (Table 2, Fig. 3 to 10).

After an acute increase of mean arterial pressure due to internal or external stress occurred during regulation, pressure continued to maintain a desired level in a few minutes (Fig. 3, 8 & 10). Since the convergence time to a set point was short relatively, we expect that the present controller can be used for a patient requiring emergency treatment.

On the basis of theoretical considerations and experimental results, we conclude that this adaptive controller will significantly improve the performance of drug infusion systems in clinical applications.

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= 국문초록 =

Sodium Nitroprusside Dihydrate와 적응 제어방식을 이용한 고혈압 가토의 혈압조절에 관한 연구

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임상에서 악성고혈압, 고혈압성 좌심실부전, 고혈압환자의 응급수술을 요하는 상황등 응급 혈압강하가 필요한 경우를 종종 접하게 된다.

이에 저자들은 고혈압이 유발된 가토를 이용하여 sodium nitroprusside dihydrate로 자동제어방식을 통한 13예의 혈압조절 실험을 한 결과 다음과 같은 결론을 얻었다.

1. 자동제어방식중 생체계 모델의 특성을 가장 잘 수렴할 수 있는 적응제어방식, 그중에서도 극지정자율조절방식 (PASTC)을 선택 적용한 모든 예에서 원하는 수준으로 혈압이 조절유지됨을 관찰하였다.

2. 혈압이 안정적으로 조절되기까지의 시간은 300—630초이고 유지된 혈압의 표준 편차는 최대 3.9 mmHg이었다.

3. 이상의 결과에서, 본 방식을 이용해 응급을 요하는 여러 임상상황에서 안전하고 안정적으로 혈압을 조절할 수 있음을 확인하였다.