An Automatic Control System of the Blood Pressure of Patients Under Surgical Operation

Eiko Furutani, Mituhiko Araki, Shugen Kan, Tun Aung, Hisashi Onodera, Masayuki Imamura, Gotaro Shirakami, and Shunzo Maetani

Abstract: We developed an automatic blood pressure control system to maintain the blood pressure of patients at a substantially low level during a surgical operation. The developed system discharges two functions, continuous feedback control of the mean arterial pressure (MAP) by a state-predictive servo controller and risk control based on the inference by fuzzy-like logics and rules using measured data. Twenty-eight clinical applications were made beginning in November 1995, and the effects of the automatic blood pressure control on the operation time and on bleeding were assessed affirmatively by means of Wilcoxon testing. This paper essentially reports the engineering details of the control system.

Keywords: Blood pressure control, clinical application, hypotensive anesthesia, risk contr ol, state-predictive servo system.

1. INTRODUCTION

The authors developed an automatic control system of the blood pressure of patients under surgical operation. The system maintains the blood pressure of patients at a substantially low level during operation using a hypotensive drug (trimethaphan camsilate). This "deliberate hypotension" reduces the intraoperative bleeding and brings about two major desirable effects. First, detailed anatomical structures in the operative field are revealed, which otherwise might be obscured by blood, and thus, a more accurate and speedy operation is facilitated. Second, blood transfusion is spared, and thus, the risk of its side effects, such as sepsis, organ failure, etc., are decreased.

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In spite of the advantages described above, deliberate hypotension is not widely practiced, because it is not easy to manipulate the infusion rate of a hypotensive solution to accurately maintain the blood pressure at a sufficiently low level above the critical limit, and because such an operation, supposing it can be performed manually, requires high level of intensive labor from the medical staff. The purpose of our study is to develop a computer control system so that the medical staff can utilize deliberate hypotension whenever they think it is appropriate, therefore avoiding the imposition of extra intensive labor on them.

Various researches have been reported concerning blood pressure control [1-12]. Sheppard [1], Widrow [2], Koivo [3, 4], Arnsparger et al. [5], Masuzawa and Fukui [7] and Fukui and Masuzawa [8] applied PID controllers, ordinary adaptive controllers, LQ-type optimal controllers and rule-based controllers, which are standard control mechanisms for delay-free plants and do not have the ability to overcome the pure delay included in the dose response. On the other hand, Woodruff [6], Pajunen et al. [9], Yu et al. [10] and Delapasse et al. [11] applied the Smith controller, an adaptive controller, a model predictive controller and a self-tuning controller respectively, which can take the pure delay of the plant into account. However, the Smith controller does not have enough disturbance rejection ability because effects of disturbances are not taken into account. Adaptive controllers and self-tuning controllers do not work well under noisy conditions, such as during surgical operations, and for them, as well as model predictive controllers, no systematic method has been established to assure the specified amounts of dead time and gain margins.

Based on the results of experiments on dogs [13], we developed a blood pressure control system, which discharges two functions: continuous feedback control of the mean arterial pressure (MAP), and risk control based on inference logics. The MAP control is carried out by the state-predictive servo mechanism, which takes the effects of pure delay into account in a very exact way and can be easily designed so that the system has sufficient disturbance rejection ability and specified amounts of dead time and gain margins in the linear-theoretic framework [14-16]. The parameters of the controller are determined based on the dose-response characteristics of the individual patient, which is identified at the beginning of the operation using a rectangular test signal. The MAP of the patient is maintained at approximately 60-75 mmHg, where the exact reference value of the MAP is determined by the medical doctor based on the condition of the patient. The risk control is carried out by the "risk control algorithm" which is a system of inference rules using measured data as well as "necessity-indices" induced from fuzzy-like logics. The risk control algorithm executes three sorts of actions: to stop infusion of the hypotensive drug, to adjust the infusion rate of the intravenous fluid, and to display risk-reducing messages with alarming sound. As risk-reducing messages, the following are incorporated at present: "administer diuretic drug," "administer vasopressor," "adjust anesthesia," "transfuse bloods (plasma protein fraction (PPF), concentrated red cell (CRC), and/or fresh frozen plasma (FFP))," pay attention to "abnormal pulse pressure," and pay attention to "abnormal oxygen saturation."

First, the safety and reliability of the system was confirmed by experiments on dogs. Then the system was clinically applied to patients undergoing major surgery. From November 1995 to July 1999, 28 clinical applications were made, where 13 of them were for total pelvic exenteration. The effects of the automatic blood pressure control on the operation time and on the bleeding were assessed affirmatively using a Wilcoxon test.

Based on the above results, the control system is clinically applied at present using a renewed system. The new system is built in a notebook-type computer with marginally modified software on the risk control algorithm. In this paper, the engineering details of the basic control algorithm are mainly reported whereas the medical details of its clinical applications have been reported elsewhere [17, 18]. The paper is organized as follows. The structure of the system is outlined in Section 2. The MAP control mechanism is explained together with its design process in Section 3, and the risk control algorithm in Section 4. Results of clinical applications are briefly introduced in Section 5. Discussions are made in Section 6 as well as comparison with previous researches [1-12].

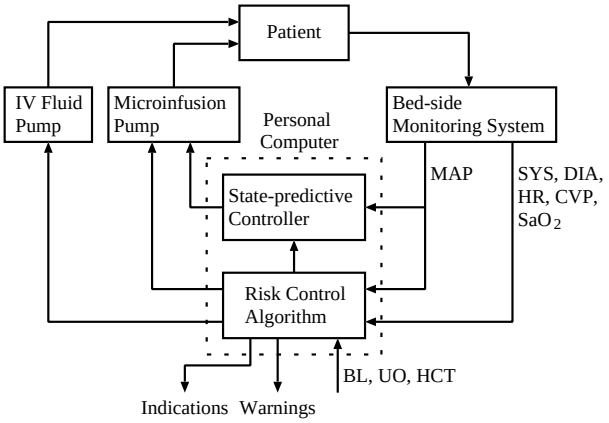

Fig. 1. Structure of the blood pressure control system. Mean arterial pressure (MAP), systolic arterial pressure (SYS), diastolic arterial pressure (DIA), heart rate (HR), central venous pressure (CVP), and oxygen saturation (SaO_2) are sent from the monitoring system to the personal computer. Blood loss (BL), urinary output (UO) and hematocrit (HCT) are input from the keyboard. The personal computer calculates and sends to the pumps the infusion rates of the hypotensive drug and intravenous (IV) fluid. It also issues indications and warnings.

The term "target MAP" will be used to indicate the reference value for MAP when clinical applications are introduced. Also, the term "pulse pressure (PP)" will be used to refer to the difference between systolic arterial pressure (SYS) and diastolic arterial pressure (DIA). These terms have been used by medical doctors and we follow their tradition.

2. OVERALL STRUCTURE OF THE SYSTEM

The structure of the system is shown in Fig. 1. The bed-side monitoring system (HP Component Monitoring System M1165A) measures mean arterial pressure, systolic arterial pressure, diastolic arterial pressure, heart rate, central venous pressure and oxygen saturation. These data are sent to the personal computer (NEC PC-9801 RA) as analog signals. The personal computer reads in the analog signals via an A/D transformer with the sampling period of 3 seconds. The control law for the MAP and the inference rules of risk control are incorporated in this computer. The state-predictive controller determines the infusion rate of the hypotensive drug, and the risk control algorithm determines the infusion rate of the intravenous (IV) fluid, and necessary risk-reducing messages. The infusion rate signals are sent out with the same sampling period (3 seconds) to the microinfusion pump (IVAC 770) and to the intravenous fluid pump (IVAC 560). The messages are displayed at the console accompa-

nied by sounds of an alarm. The microinfusion pump infuses the hypotensive drug and the intravenous fluid pump infuses the intravenous fluid, respectively, at the rates sent from the computer. Measurements of blood loss, urinary output and hematocrit are input to the computer manually from the keyboard.

To summarize from the viewpoint of control engineering, the detected variables are mean arterial pressure (MAP), systolic arterial pressure (SYS), diastolic arterial pressure (DIA), heart rate (HR), central venous pressure (CVP), oxygen saturation (SaO_2), blood loss (BL), urinary output (UO) and hematocrit (HCT). The first 6 variables are sampled with the sampling period of 3 seconds, BL and UO with the period of 30-60 minutes, and HCT with the period of 1-2 hours. For the continuous feedback control of MAP, only the measured value of MAP is used. For risk control, which includes stopping of the hypotensive drug infusion, manipulation of the intravenous fluid, and messaging, all the measurements are utilized.

3. FEEDBACK CONTROL OF MAP (MEAN ARTERIAL PRESSURE)

3.1. Model of the response of MAP to the hypotensive drug infusion

In our system, trimethaphan camsilate is used as a hypotensive drug. It is a ganglion blocker and was chosen because of its effect and safeness (ref. to [19] for details). The model of the response of MAP to infusion of the hypotensive drug was constructed from experiments on dogs, which were performed according to the institutional guidelines of Kyoto University for the care and use of laboratory animals.

Based on the dose-responses under the administration of the hypotensive drug at three constant rates for two dogs, a dynamical model was constructed (ref. to [13] for details), whose exact form in the range where the state variable x is small is as follows:

$$\frac{dx(t)}{dt} = -\frac{1}{T}x(t) + \frac{K}{T}u(t), \tag{1}$$

$$y(t) = x(t-L), \tag{2}$$

$$T = \begin{cases} T_1 & dx/dt \geq 0 \\ T_2 & dx/dt < 0 \end{cases}.$$

Here, x is the state variable, u is the infusion rate of the hypotensive drug, y corresponds to the MAP, K, L, T_1 and T_2 are constants and dependent on the individual as well as on its condition. The parameters K, L, T_1 and T_2 for dogs are within the ranges of Table 1, whereas T_1 is always smaller than T_2 for each case. We assume that the response of human blood pressure can be modeled as the same form with different parameter values. From the identification results before clinical application, the parameters K, L and T_1 for humans are estimated within the ranges of Table 2. (Here, the range of T_2 is not shown because T_2 is not used for designing our control system as discussed in Subsection 3.2, whereas the relation of T_1 and T_2 is estimated to remain the same.) The model given by (1) and (2) is used for the design of the controller of MAP. In designing the controller for each patient, the parameters of the patient obtained by a simple identification are used, but, when the parameters of the individual patient cannot be obtained, the parameter values of Table 3 are used so that the designed control system has adequate robustness (we discuss the choice of the parameters in Subsections 3.2 and 3.4). As for the details of the modeling process and the global model, refer to [13].

Table 1. Parameters of dogs.

K	2.0-4.5	mmHg kg min/μg
T_1	1.50-3.33	min
T_2	4.50-8.33	min
L	0.50-0.67	min

Table 2. Parameters of patients.

K	2.0-20.0	mmHg kg min/μg
T_1	3.33-10.0	min
L	0.67-1.00	min

Table 3. Default values of parameters for design.

K	20.0	mmHg kg min/μg
T	3.33	min
L	1.00	min

3.2. Design strategy

The response model of MAP to infusion of the hypotensive drug obtained as above includes a dead time. To cope with this dead time, we chose the state-predictive servo mechanism [14, 20]. The state-predictive servo mechanism is a controller with observer-based state feedback, which takes the dead time of plants into account. (Refer to [14-16] for general structures, stability, robustness, etc. of this type of controllers.)

Another difficulty with the response model of MAP is the derivative-dependent nonlinearity; i.e. the fact that the time constant T in (1) changes its value depending on the sign of the derivative of the state variable. There has not been developed, up to now to the authors' knowledge, an effective control method that takes this sort of nonlinearity into account positively. So, we decided to design a controller in the linear-theoretic framework and to reserve "enough amount of robustness" in order to cope with the above nonlinearity. From this viewpoint, we assumed:

(i) The dead time L in (2) is a multiple of the sampling period T_0 (three seconds in clinical application); i.e.

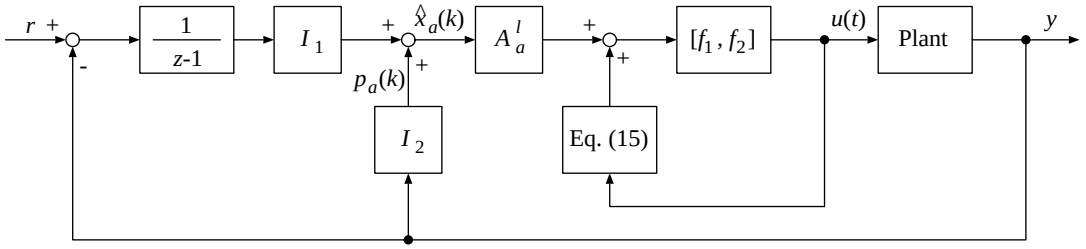

Fig. 2. State-predictive servo system. r is a reference input, $u(k)$ is a manipulated input and y is a controlled output. Eq. (15) is a finite interval summation for state prediction.

$$L = lT_0 \quad l: \text{positive integer} \tag{3}$$

If this assumption is not satisfied, we set the dead time as the minimum multiple, which is not smaller than the actual dead time.

(ii) The T of (1) takes the smaller value of T_1 and T_2 regardless of the sign of the derivative of x; i.e.

$$T = T_1 \tag{4}$$

The rationale for the above assumptions is as follows. In the design of the state-predictive servo mechanism, it is possible to choose the parameters so that the closed-loop system exhibits "strong robust stability," i.e. it is stable for negative modeling errors of the gain and the dead time. Taking into account the fact that the dead time gives the severest phase displacement, we can say the strong robust stability approximately implies, in the case of a scalar control system, that the closed-loop system remains stable for negative gain and positive phase displacements in the plant model. Thus, we can expect that the linear closed-loop system remains stable for all possible values of time-constants, dead times, and gains if we use the model with the smallest possible time-constant, the longest possible dead time and the largest possible gain and if the controller is designed to be strongly robust stable. In reality, the plant is nonlinear and therefore, robust stability is not rigorously guaranteed. However, the stability conditions for nonlinear feedback systems such as the circle criteria suggest that it is very plausible that the real system remains stable. Our numerous simulation results strengthen the plausibility of this suggestion.

3.3. Structure of state-predictive controllers

In various references (e.g. [14, 20]), state-predictive controllers are discussed in the continuous-time setting. But in our application, we need to use a digital controller. That being the case, we briefly formulate a digital version of the state-predictive controllers here. Discretizing (1), (2) with the sampling period T_0, we obtain

$$x(k+1) = ax(k) + bu(k), \tag{5}$$

$$y(k) = x(k-l), \tag{6}$$

where

$$a = e^{-T_0/T}, \quad b = K(1 - e^{-T_0/T}).$$

We introduce an integrator in order to endow the system with robust tracking ability. Denoting the state variable of the integrator by $x_I(k)$, we obtain the next equation of the augmented system

$$\begin{aligned} x_a(k+1) &= A_a x_a(k) + B_a u(k), \\ y(k) &= C_a x_a(k-l), \end{aligned} \tag{7}$$

where

$$x_a(k) = \begin{bmatrix} x_I(k) \\ x(k) \end{bmatrix}.$$

The coefficient matrices of the augmented system are given by

$$A_a = \begin{bmatrix} 1 & -\alpha \\ 0 & a \end{bmatrix}, \quad \alpha = T(1 - e^{-T_0/T}), \tag{8}$$

$$B_a = \begin{bmatrix} \beta \\ b \end{bmatrix}, \quad \beta = KT(1 - e^{-T_0/T} - \frac{T_0}{T}), \tag{9}$$

$$C_a = \begin{bmatrix} 0 & 1 \end{bmatrix}. \tag{10}$$

We choose a feedback gain

$$F_a = \begin{bmatrix} f_1 & f_2 \end{bmatrix} \tag{11}$$

for the augmented system so that $A_a - B_a F_a$ is stable.

Next, we usually introduce an observer that estimates the delayed state $x(k-l)$. However, since the lumped parameter part of the plant model is a first-order system in this case, $y(k)$ is nothing but $x(k-l)$ itself (see (6))[1]. Therefore, the estimate of the state variable of the augmented system at time $k-1$ is given by

$$\hat{x}_a(k-l) = \begin{bmatrix} v_I(k) \\ y(k) \end{bmatrix}, \tag{12}$$

where $v_I(k) = x_I(k-l)$ is an integration of the error

[1] $\hat{x}(k-l) = y(k)$ ($\hat{x}$: estimate of x) can be regarded as a minimal-order observer for the lumped parameter part of the plant.

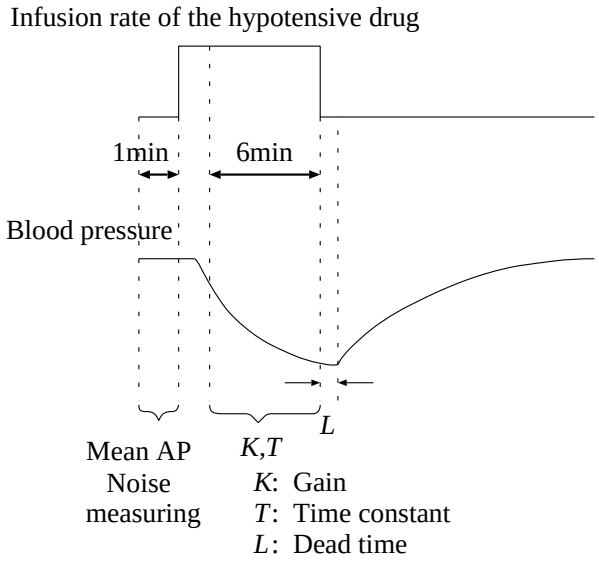

Fig. 3. Identification method of individual parameters. From the MAP data for the first minute, the initial MAP and the maximal noise are determined. From the MAP data for 6 minutes after the MAP becomes low enough, the individual parameters K, T and L are determined.

between the reference input $r(k)$ and the output $y(k)$ given by

$$v_1(k) = \sum_{i=0}^{k-1} \{r(i-l) - y(i)\} + \sum_{i=k}^{k+l-1} r(i-l). \quad (13)$$

Adding the effect of the input from time $k-l$ to time $k-1$, we can obtain the estimate of the state of the augmented system at time k as

$$\hat{x}_a(k) = A_a^l \begin{bmatrix} v_1(k) \\ y(k) \end{bmatrix} + p_a(k), \quad (14)$$

with

$$p_a(k) = \sum_{i=k-l}^{k-1} A_a^{k-i-1} B_a u(i). \quad (15)$$

The manipulated input $u(k)$ is set to

$$u(k) = \begin{bmatrix} f_1 & f_2 \end{bmatrix} \hat{x}_a(k). \quad (16)$$

The structure of the obtained system is shown in Fig. 2, where

$$I_1 = \begin{bmatrix} 1 \\ 0 \end{bmatrix}, I_2 = \begin{bmatrix} 0 \\ 1 \end{bmatrix}. \quad (17)$$

3.4. Identification scheme

The dose-response characteristics of MAP to the hypotensive drug depend on the individual patient, and the range of parameter variations is estimated to be fairly large as provided in Table 2. Even under this

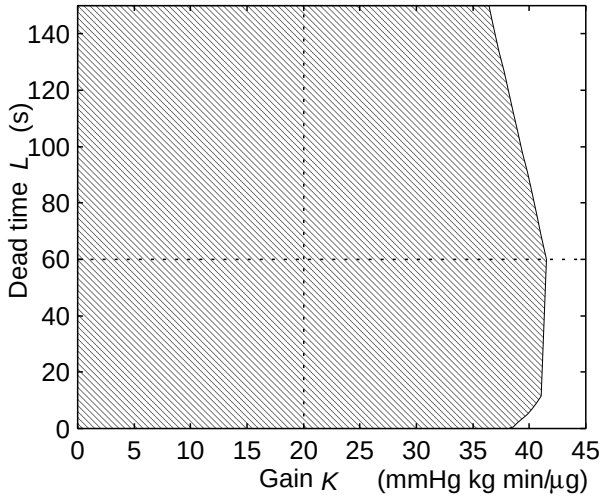

Fig. 4. Stability region in the gain-dead time plane of the blood pressure control system.

circumstance we can expect the designed system to remain stable as explained in Subsection 3.2. However the performance of the control system, such as response speed, damping ratio and disturbance rejection, deteriorates roughly in proportion to the difference between the actual parameters and the assumed ones. To lessen such deterioration, we have adopted the following strategy:

(i) Identify the dose-response of each patient just before the surgery by applying a simple test input, which does not give any negative effect to the physiological state of the patient.

(ii) Use the time-constant, the dead time, and the gain deduced from the test, if they are reliable, that is, if they are within the parameter ranges in Table 2 respectively, and if noise and disturbances do not have a great influence on the response of MAP to the test input. Otherwise, use the smallest plausible time-constant, the longest plausible dead time, and the largest plausible gain.

As the test input for identification, we use a rectangular signal as shown in Fig. 3. The parameters K, T, and L of each patient are identified from the response curve of MAP to this input signal. In order to reduce the influence of the measurement noise, the filtered value $y_{\mathrm{Id}}(k)$ of $y(k)$ as given by

$$y_{\mathrm{Id}}(k) = \{y(k-2) + 4y(k-1) + 6y(k) + 4y(k+1) + y(k+2)\}/16 \quad (18)$$

is used as the data for identification. The form of the above filter was selected by trial-and-error so that the MAP elevation by measurement noise is undetected and the time of MAP elevation after stopping the hypotensive drug can be detected against noise. It should be noted that the dead time L cannot be determined accurately from the rise-up part (note that "rise-up" means "decreasing" in this case) of the dose-response,

because it is difficult to fill the cannula with the solution of the hypotensive drug completely before identification. Considering this fact, we determine the dead time L using the close-down part of the response.

The entire identification procedure is as follows. As a preliminary step, MAP is measured for 60 seconds before infusion of the hypotensive drug. Based on the data of these 60 seconds, the normal MAP of the patient and the maximal amplitude of the measurement noise are calculated (in the following, we call them the *initial MAP* and the *maximal error*, respectively). Following the above preliminary measurement, we initiate the identification test. First, the hypotensive drug is infused at 3 μg/kg/min. If the MAP becomes lower than $y_{\text{thre}} :=$ (initial MAP) – (maximal error) in five minutes, the infusion is continued for another 6 minutes and the measured MAP data is used for identification. If not, infusion of the hypotensive drug is stopped temporarily until the MAP is elevated nearly back to the initial MAP (e.g. within 3 mmHg of the initial MAP). Then the same procedure is repeated once again at a higher rate (e.g. 5 μg/kg/min) of infusion. If the MAP does not become lower than the new y_{thre} (:= (new initial MAP) – (new maximal error)) in five minutes this time either, identification testing is called off. In the above process, infusion of the hypotensive drug is stopped whenever MAP becomes lower than the level which is estimated to cause danger for the patient, and identification testing is immediately halted.

If a satisfactory data is obtained from the test described above, gain K and the time-constant T are calculated by the least mean square method using the data from the time when the MAP becomes lower than y_{thre} to the time when infusion of the hypotensive drug is stopped (Fig. 3). The dead time L is determined as the time between the stopping of infusion of the hypotensive drug and the beginning of elevation of MAP (Fig. 3). If a satisfactory data is not obtained from the test, we use the default values as given in Table 3. When the obtained values of the parameters are not within the ranges of Table 2, we repeat identification if time permits. Otherwise, we also use the default values. The default values of Table 3 were determined from Table 2 as follows:

T: the smallest value of T

K: the largest value of K

l: dividing the longest value of L by T_0 and rounding up the result to the next whole integer

By using these values, we can design a control system that is strongly robust stable in the linear-theoretical framework as explained in Subsection 3.2.

3.5. Design of the controller

We first designed a control system for the default values of parameters under the specification

Settling time T_s: $5 \le T_s \le 20$ (min)

Overshoot: less than 20%

Robust stability: "strong robust stability" mentioned in Subsection 3.2.

By repeating trial-and-errors, we obtained a control system with the poles of the augmented system being at 0.970 and 0.985 (-0.6 and -0.3/min in the continuous time scale). That is, F_a was determined so that the eigenvalues of $A_a - B_a F_a$ were 0.970 and 0.985. The stability region of this control system in the gain-dead time plane was calculated using the method of [15, 16] and found to be large enough (Fig. 4).

Based on the above off-line design, we decided to carry out the on-line (automatic) design as follows. If the parameters of the patient are identified satisfactorily, the controller is determined by assigning the poles of the augmented system at the above positions (i.e. 0.970 and 0.985) to obtain better response than that designed using the default values. Otherwise (i.e. if we have to use the default values), we use the controller obtained in the off-line design.

3.6. Auto-tuning of the controller gain

The response of MAP to infusion of the hypotensive drug is changed slowly during surgical operation. This means that the mismatch between the model and the dose-response characteristics of the real patient becomes greater. To cope with this variation, the controller gain is tuned when the infusion rate of the hypotensive drug is neither equal to the maximal infusion rate (20 μg/kg/min in clinical application usually) nor 0. Auto-tuning rules are determined by using the results of animal experiments [13] and by modifying them so that the infusion rate decreases quickly enough when blood pressure decreases. The rules are as follows. Here, r is a constant target level of the MAP.

- If the MAP is lower than $r-6$ mmHg, then the controller gain is divided by 1.2 every 60 s. If the MAP is between $r-6$ and $r-4$ mmHg, then the controller gain is divided by 1.1 every 60 s.
- If the MAP does not become lower than the ((initial MAP) + (the target MAP))/2 within 5 min, then the controller gain is multiplied by 1.2.
- After 5 min, if the MAP is not lower than $r+10$ mmHg, then the controller gain is multiplied by 1.2 every 90 s. If the MAP is between r + 5 and r + 10 mmHg, then the controller gain is multiplied by 1.1 every 90 s.

4. RISK CONTROL ALGORITHM

The patient is not always safe under surgical operation even when his/her MAP is maintained at the desired level. In order to prevent the patient from lapsing

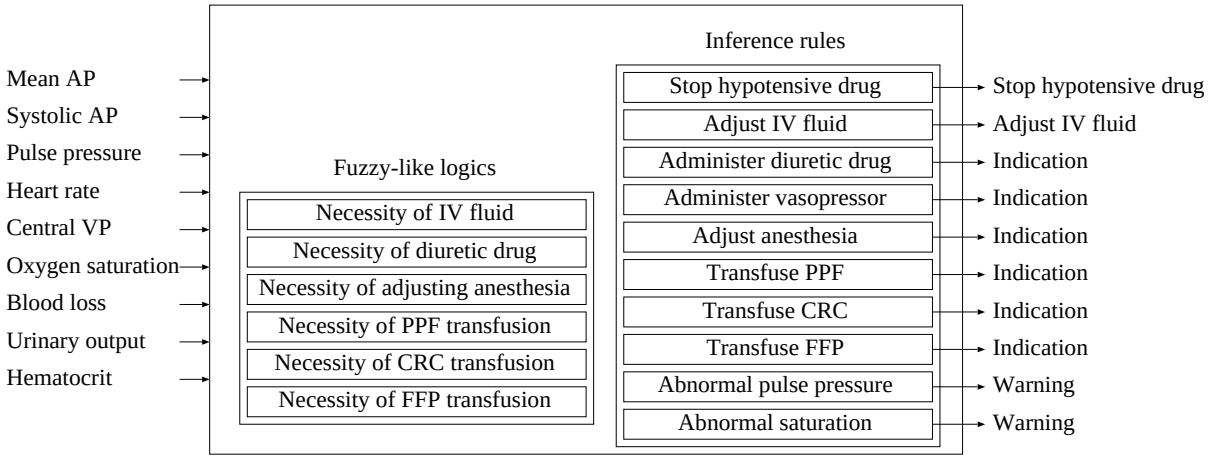

Fig. 5. Risk control algorithm. In the first step, necessity indices for six treatments are calculated by fuzzy-like logics. In the second step, taking those necessity indices into account and using the measurement data directly, the actions to be taken are determined.

into a dangerous state, we developed a "risk control algorithm," which infers the patient's condition, and executes three sorts of actions: stops infusion of the hypotensive drug, adjusts the infusion rate of the intravenous fluid, and issues risk-reducing messages. The messages are classified into "indications" and "warnings," where an "indication" is a message that suggests some concrete countermeasures to reduce the risk and a "warning" is a message that only informs of existence of the risk. In this section, we explain the risk control algorithm together with its design process.

4.1. Hearing investigation of risk-reducing treatments

In order to develop an appropriate risk control algorithm, we carried out a hearing investigation of risk-reducing treatments from three anesthesiologists in Kyoto University Hospital. The anesthesiologists were qualified as Diplomats of The Board of Japan Society of Anesthesiology and had experience in administering patients during surgical operation for more than ten years. We asked them about the following points:

1. patient's conditions regarded as "dangerous," when the patient's blood pressure is kept at a low level,
2. measurement data used for judging the above conditions, and
3. treatments for each "dangerous" condition.

Based on their advices, we determined measurement data to use, membership functions to carry out fuzzy-like induction, and inference rules. Membership functions and inference rules were determined as follows. For example, the anesthesiologists' empirical rules based on systolic arterial pressure were shown in Table 4. Systolic arterial pressure was divided into various ranges, so we selected a triangular or trapezoid type membership function according to the width of the range for each range. We determined tentative membership functions for measurements through the same procedure. Next, we made tentative inference rules by describing each empirical rule using the tentative membership functions. Then, we fedback the results of inference obtained by our algorithm to the anesthesiologists, and repeated improvements until our results agreed with the anesthesiologists' judgments.

4.2. Outline of the risk control algorithm

The measurement data used for risk control are mean arterial pressure (MAP), systolic arterial pressure (SYS), pulse pressure (PP), heart rate (HR), central venous pressure (CVP), oxygen saturation (SaO_2), blood loss (BL), urinary output (UO) and hematocrit (HCT), where the pulse pressure (PP) is not a "directly measured" data but obtained as the difference between the systolic arterial pressure and the diastolic arterial pressure (DIA). Based on these measurements, the risk control algorithm infers the patient's condition and takes the following actions: stops infusion of the hypotensive drug, adjusts the infusion rate of intravenous fluid, and issues risk-reducing messages. The messages are classified into "indications" and "warnings," as stated at the beginning of the section. Indications are "administer diuretic drug," "administer vasopressor," "adjust anesthetic drug density" and "transfuse bloods (PPF, CRC, and/or FFP)." Warnings are "abnormal pulse pressure," and "abnormal oxygen saturation." When the algorithm displays indications or warnings, an alarm is sounded.

The risk control algorithm consists of two steps. In the first step, necessity indices for adjustment of intravenous fluid, administration of the diuretic drug, adjustment of anesthetic drug density, transfusion of plasma protein fraction (PPF), transfusion of concentrated red cell (CRC), and transfusion of fresh frozen plasma (FFP) are calculated by fuzzy-like logics.

In the second step, taking those necessity indices

Table 4. Example of the anesthesiologists' empirical rules (based on systolic arterial pressure (SYS)).

SYS (mmHg)	Treatment
180-	Infuse hypotensive drug.
150-180	If heart rate is high, increase anesthetic drug density. Consider infusion of hypotensive drug.
80-150	Take no action.
70-80	Decrease anesthetic drug density.
60-70	Stop anesthesia. Administer vasopressor.
50-60	Use O_2 only. Administer vasopressor.
-50	Administer catecholamine.

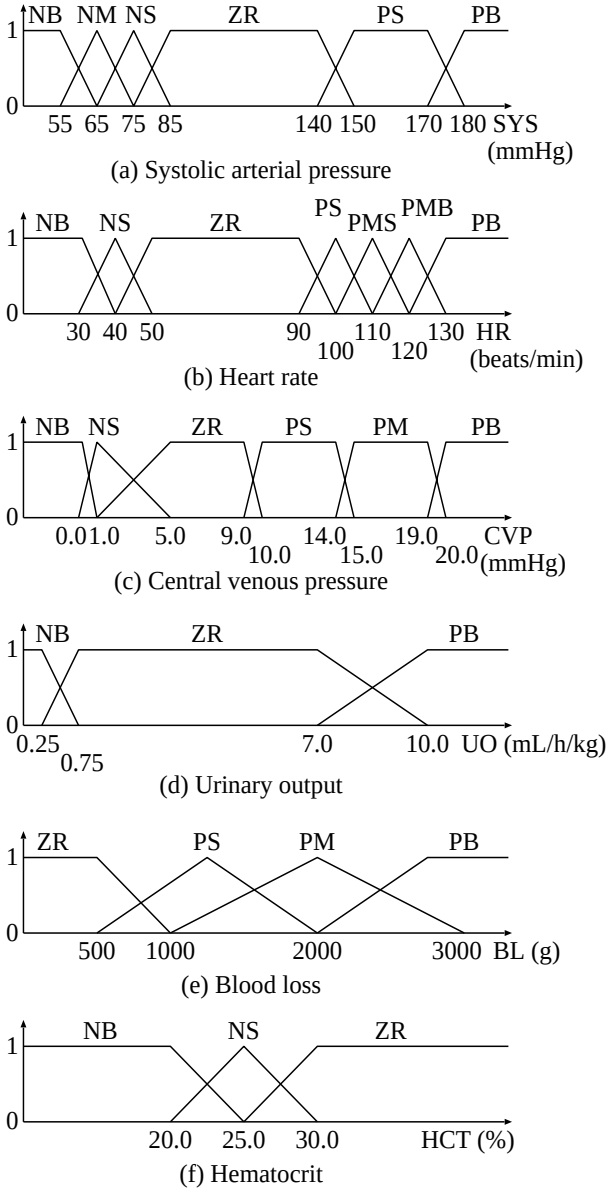

Fig. 6. Membership functions. P, N, ZR, B, M and S stand for 'positive', 'negative', 'zero', 'big', 'medium' and 'small', respectively.

Table 5. Logics of calculating the necessity index f_{IV} for adjusting the intravenous fluid infusion rate.

If (HR=PS or PMS or PMB or PB) and (SYS=NS or NM or NB), $f_{IV}=1$.
If CVP=NB, $f_{IV}=1$.
If CVP=ZR and UO=NB, $f_{IV}=1$.
If time $\geq$ 120 min and UO=PB, $f_{IV}=-1$.

into account and also using the measurement data directly, the actions to be taken are determined. The overall structure of the risk control algorithm is shown in Fig. 5, where the details will be explained in the following subsections.

4.3. Calculation of necessity indices by fuzzy-like logic

As an example, adjustment of the infusion rate of intravenous fluid will be explained in detail, where its necessity index will be denoted by f_{IV}. To determine f_{IV}, we use systolic arterial pressure, heart rate, central venous pressure, and urinary output.

First, the measured data are converted to fuzzy variables by the membership functions shown in Fig. 6. The results are stored as SYS, HR, CVP and UO, which are assigned the values PB, PS, ZR, NS, NB, etc. with the confidence rate equal to the height of the membership function, as shown above the membership function in Fig. 6. Here, 'P' stands for 'positive', 'N' stands for 'negative', 'ZR' stands for 'zero', 'B' stands for 'big', 'M' stands for 'medium' and 'S' stands for 'small'. In combination, for instance, PB implies "positive big," NS implies "negative small," etc.

Then, f_{IV} is calculated by the fuzzy rules given in Table 5. The algebraic product-sum method [21], which is the method obtained by replacing minimization with algebraic product and maximization with summation in the min-max method [22], is used for this calculation. As a result, f_{IV} can take values outside [0,1]. In the standard fuzzy logic, a more sophisticated scheme is used for the calculation of f_{IV} in order to confine its value to the range [0,1]. But for our purpose, we only need to know the necessity of adjusting the infusion rate, and f_{IV} taking values outside [0,1] does not cause any inconvenience. The more important factor to our purpose is easiness of adjusting membership functions so that the final results agree with anesthesiologists' judgments. To this end, the algebraic product-sum method seemed to be most appropriate, because the effects of changes in membership functions can be easily (and intuitively) predicted by the anesthesiologists themselves. The

necessity indices f_{diur} for administration of the diuretic drug, f_{anesth} for adjusting anesthetic drug density, f_{PPF} for transfusion of PPF, f_{CRC} for transfusion of CRC and f_{FFP} for transfusion of FFP are calculated in the same way by the rules given in Tables 6, 7, 8, 9 and 10, respectively.

4.4. Determination of treatments

The measures taken by the risk control algorithm are:

(On-line Control)

- to stop infusion of the hypotensive drug,
- to adjust the infusion rate of IV fluid,

(Indications)

- to display the indication "administrate diuretic drug,"
- to display the indication "administrate vasopressor,"
- to display the indication "adjust anesthetic drug density,"
- to display the indication "transfuse PPF, CRC and/or FFP,"

(Warnings)

- to display the warning "abnormal pulse pressure," and
- to display the warning "abnormal oxygen saturation."

When an "indication" or "warning" is displayed, an alarm is sounded.

The actions to be taken and the treatments to be included in "indications" are determined by logical inference rules using both the original measurement data and the necessity indices. Schemes are also incorporated into the algorithm enabling the doctor (assuming an anesthesiologist) to intervene the inference process. The details of the inference logics are as follows.

The most important treatments of the risk control algorithm are to stop infusion of the hypotensive drug and to indicate administration of vasopressor when the blood pressure becomes too low. The rules of inference for these treatments are shown in Tables 11 and 12. When infusion of the hypotensive drug is stopped, the integration of the error between the target MAP and the patient's MAP is stopped to avoid reset windup, while the prediction of state is continued by the prediction mechanism. When the controller is restarted, the state of the integrator at stopping infusion and the predicted state are used.

Table 6. Logics of calculating the necessity index f_{diur} for the administration of the diuretic drug.

If (CVP=PM or PB) and (time $\geq$ 120 min and UO=NB), $f_{diur}=1$.
If (CVP=PM or PB) and (SYS=PS or PB), $f_{diur}=1$.

Table 7. Logics of calculating the necessity index f_{anesth} for adjusting anesthesia concentration.

If (SYS=PS or PB) and (HR=PS or PMS or PMB or PB), $f_{anesth}=1$.
If (SYS=PS or PB) and CVP=PS, $f_{anesth}=1$.
If SYS=NS and (HR=PS or PMS or PMB or PB), $f_{anesth}=1$.
If (SYS=NM or NB), $f_{anesth}=-1$.
If HR=NB, $f_{anesth}=-1$.

Table 8. Logics of calculating the necessity index f_{PPF} for PPF transfusion.

If (BL=PS or PM or PB), $f_{PPF}=1$.
If UO=NB, $f_{PPF}=1$.
If CVP=NB, $f_{PPF}=1$.

Table 9. Logics of calculating the necessity index f_{CRC} for CRC transfusion.

If HCT=NB, $f_{CRC}=1$.
If HCT=NS and UO=NB and (CVP=NS or NB), $f_{CRC}=1$.
If BL=PB, $f_{CRC}=1$.

Table 10. Logics of calculating the necessity index f_{FFP} for FFP transfusion.

If (BL=PM or PB), $f_{FFP}=1$.

Table 11. Rules for stopping infusion of hypotensive drug.

Stop infusion of hypotensive drug if one of the following conditions is satisfied.
(i) MAP $\leq$ (target MAP) - 5.0 mmHg
(ii) SYS $\leq$ 70.0 mmHg or SYS $\geq$ 150 mmHg
(iii) $\frac{d(\text{MAP})}{dt} \leq -\frac{7\ \text{mmHg}}{3\ \text{samples}} = -\frac{7\ \text{mmHg}}{0.15\ \text{min}}$
(iv) HR $\leq$ 40.0 beats/min or HR $\geq$ 140 beats/min
(v) CVP $\leq$ 2.0 mmHg or CVP $\geq$ 15 mmHg
(vi) After two hours from starting operation, UO=0 or UO $\geq$ 10 mL/kg

Table 12. Rule for administration the vasopressor.

If SYS $\leq$ 70.0 mmHg, then "Administer vasopressor"

Table 13. Rules to adjust the infusion rate of intravenous fluid.

The infusion rate IV of intravenous fluid is determined by: $IV=\max(IV_a, IV_b)+IV_c$, where IV_a, IV_b and IV_c are given as follows.
(i) The basal infusion rate IV_{base} is (w+50.0) mL/h before laparotomy, and (2w+100.0) mL/h after laparotomy, where w kg is the patient's body weight.
(ii) The infusion rate IV_a corresponding to the necessity index f_{IV} is set to $IV_a = 3 \times IV_{base}$ for $f_{IV} \geq 1.2$ $IV_a = 2 \times IV_{base}$ for $0.8 \leq f_{IV} < 1.2$ $IV_a = IV_{base}$ for $f_{IV} < 0.8$.
(iii) The infusion rate IV_b corresponding to excessively low values of MAP is set to $IV_b = 999$ mL/h (max) for MAP ≤ 50 mmHg $IV_b = 2 \times IV_{base}$ for MAP $\leq$ target MAP $\times 0.85$.
(iv) If the blood loss (BL) is less than 1,000 g, the intravenous fluid equal to the increment of BL is infused in 5 min whenever a new value of BL is input manually. As a result, the infusion rate IV_c corresponding to BL is set to IV_c = (Increment of BL)/(5 min) for the 5 min after the manual input of the BL data. If IV_c is larger than 480 mL/h, then IV_c is set to 480 mL/h and the infusion period is set to ((Increment of BL)/8.0) min. If the blood loss is more than 1,000 g, IV_c is set to 0.

The infusion rate of intravenous fluid is determined as follows. First, the basal infusion rate IV_{base} [mL/h] is determined by[2]

$$IV_{base} = \begin{cases} w + 50.0 & \text{(before laparotomy)} \\ 2w + 100.0 & \text{(after laparotomy)} \end{cases} \quad (19)$$

where w [kg] is the patient's body weight. Then, it is adjusted according to the rules of Table 13, which take into account the necessity index f_{IV}, the amount of the blood loss, and the anesthesiologist's judgment totally.

The indication "Administrate diuretic drug" is displayed when the necessity index f_{diur} for administration of the diuretic drug is larger than or equal to 1.0.

The other messages are displayed in a similar way, e.g. the messages regarding adjusting anesthesia drug density are displayed according to the value of the necessity index f_{anesth} as follows:

"Increase anesthetic drug density" when $1.0 < f_{anesth}$]

"Decrease anesthetic drug density" when $-1.0 \leq f_{anesth} \leq -0.75$

[2] Usually, IV_{base} is determined in proportion to the patient's body weight w [kg], e.g., 2w [mL/h] before laparotomy and 4w [mL/h] after laparotomy. However, according to advice from the doctors who used our blood pressure control systems, IV_{base} is set as (19) at present in order to avoid the over-infusion of intravenous fluid.

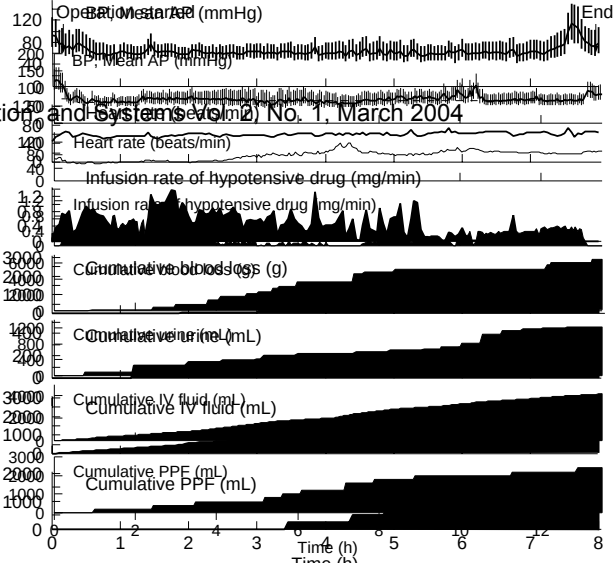

Fig. 7. A result of clinical application (April 15, 1997). Blood pressure (BP) is shown in the graph at the top. The top and the bottom of a bar show systolic arterial pressure and diastolic arterial pressure, respectively, and the solid line indicates mean arterial pressure (Mean AP).

Fig. 8. Another result of clinical application (April 21, 1998). Blood pressure (BP) is shown in the graph at the top. The top and the bottom of a bar show systolic arterial pressure and diastolic arterial pressure, respectively, and the solid line indicates mean arterial pressure (Mean AP).

Table 14. Results of blood pressure control for operations of total pelvic exenteration.

Date	T_s (min)	A_o (mmHg)	T-MAP (mmHg)	M-MAP (mmHg)	A-MAP (mmHg)	S.D. (mmHg)	C-time (min)	Duration (min)	Ope-time (h:m)	BL (g)	CRC (unit)	FFP (unit)
30/11/95	19.2	8	60	60	60.7	7.5	410.8	39.8	7:55	3800	4	10
1/2/96	7.6	5	60	60	53.9	10.0	558.2	17.3	12:12	7770	24	38
21/3/96	11.4	8	60	60	62.4	6.8	887.3	47.7	17:27	5440	15	24
28/11/96	24.5	5	60	60	62.6	9.3	646.8	46.1	13:22	3700	2	0
5/12/96	7.0	4	60	60	58.9	5.4	279.1	49.2	9:38	3035	10	8
6/3/97	34.1	10	65	65	68.2	8.3	864.4	41.9	16:00	3000	14	8
15/4/97	9.3	8	70	65	67.1	8.0	520.4	38.6	13:10	6700	15	8
14/4/98	10.7	5	60	65	65.7	5.2	316.4	49.3	10:30	1760	2	0
21/4/98	10.0	9	70	60	61.3	4.5	403.8	55.1	8:45	3600	0	0
18/6/98	6.9	6	70	65	65.6	11.6	533.9	31.3	11:30	7000	20	2
13/10/98	7.6	4	70	65	69.8	6.5	421.5	36.0	12:43	13910	32	12
24/6/99	11.0	4	75	60	60.2	2.6	93.3	57.5	6:55	1200	0	0
27/7/99	33.7	3	65	60	63.9	6.1	125.9	39.0	9:23	2500	7	4
Mean	14.8	6.2	65.0	61.9	63.1	7.1	466.3	42.2	11:30	4880	11.2	8.8
St. dev.	9.5	2.2	5.2	2.4	4.1	2.3	232.9	10.2	3:05	3390	9.6	10.7

T_s: Settling time
A_o: Overshoot
T-MAP: Initial target MAP
M-MAP: Longest maintaining target MAP
A-MAP: Averaged MAP in maintaining M-MAP
S.D.: Standard deviation of MAP from A-MAP
C-time: Time of controlling MAP at M-MAP
Duration: Time per hour that the actual response is inside $\pm$10% of the target MAP
Ope-time: Operation time
BL: Total amount of blood loss
CRC: Total transfusing amount of concentrated red cells
FFP: Total transfusing amount of fresh frozen plasma

"Stop anesthetic drug" when $f_{\text{anesth}} < -1.0$.

As warnings about pulse pressure, the following messages are displayed according to the measured value PP of the pulse pressure:

"Pulse pressure is small." when PP < 25 mmHg

"Pulse pressure is too small. Raise the target MAP." when PP < 20 mmHg.

As a warning about oxygen saturation, the following message is displayed:

"Oxygen saturation is small." when SaO_2 < 95%.

It should be noted that the final decisions of treatments except for stopping infusion of the hypotensive drug and adjusting the infusion rate of IV fluid are made by anesthesiologists considering the messages and other information including that which is not considered in our risk control algorithm.

4.5. Countermeasures against electric knife and noxious stimulation

In addition to taking the above actions, the system is designed to cope with the electromagnetic noise caused by an electric knife and with the rapid increase of blood pressure caused by noxious stimulation during incision. To cope with the electromagnetic noise caused by an electric knife, the system includes the rule: "when the difference of the current heart rate from that at three seconds before is more than 20 times/min, do not use the measured value of the current heart rate as the input to the risk control algorithm." To cope with the rapid increase of blood pressure caused by noxious stimulation during incision, the system includes the following scheme. Namely, by pushing a button when the incision is started, the upper limit is set for the infusion rate of the hypotensive drug to the value obtained by averaging the infusion rates during the last nine seconds (i.e. three sampling periods).

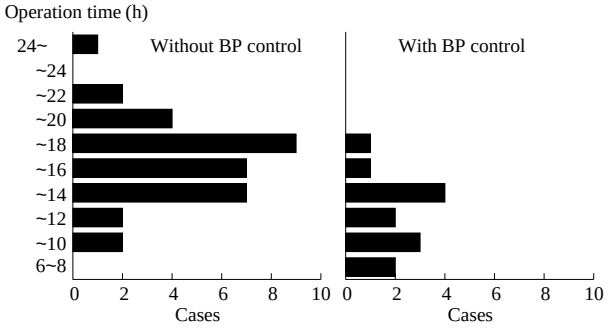

Fig. 9. Comparison of operation times of total pelvic exenteration with blood pressure (BP) control (13 cases) to those without BP control (34 cases).

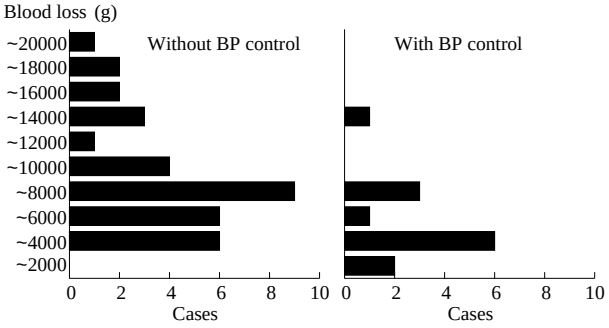

Fig. 10. Comparison of blood loss during operations of total pelvic exenteration with blood pressure (BP) control (13 cases) to those without BP control (34 cases).

5. CLINICAL APPLICATIONS

With the approval by the Ethics Committee of Kyoto University Hospital, 28 clinical applications were made from November 1995 to July 1999. In all cases, the results of blood pressure control were positively appreciated by the medical doctors who performed the operations. The target MAPs were set by the doctors between 60 and 75 mmHg according to patients' clinical conditions. The typical results of blood pressure control are shown in Figs. 7 and 8. In the figures, blood pressure, MAP, heart rate, infusion rate of the hypotensive drug, cumulative blood loss, cumulative urinary output, cumulative intravenous fluid and cumulative PPF are shown. The patients were a 50 year old male and a 46 year old male, respectively, who had local recurrence of rectal carcinoma. Total pelvic exenteration was performed on both patients. MAPs were maintained at 65 mmHg and at 60 mmHg, respectively. (In the latter case, the target MAP was set to 70 mmHg at first, and changed several times according to indications of the medical doctor.) In order to avoid overinfusion of the hypotensive drug in response to sudden rise in blood pressure due to external disturbances at the beginning of the operation, the MAP control was started after the opening of the abdomen. The settling times and overshoots were 9.3 min and 10.0 min, and 8 mmHg and 9 mmHg, respectively. The total amounts of blood loss were 6,700 g and 3,600 g, and the operation times were 13 hours 10 minutes and 8 hours 45 minutes, respectively. Fifteen units of CRC and eight units of FFP were transfused in the former case, while no blood transfusion was necessary in the latter case.

In Table 14, the settling time, the overshoot, the initial reference value of MAP, the reference value of MAP maintained for the longest time (this value is denoted as M-MAP), the averaged MAP during the period maintaining M-MAP (denoted as A-MAP), the standard deviation of MAP from A-MAP, the time of controlling MAP at M-MAP, the duration (i.e. the averaged time in minutes when the error is less than 10% for each hour), operation time, total amount of blood loss, and total transfusion amount of CRC and FFP are shown for 13 cases of total pelvic exenteration. Also, to show the performance of our system, the averaged settling time, the averaged overshoot and the averaged duration for the entire clinical applications (28 cases up to July 1999) are given in Table 15. Furthermore, the averaged settling time in changing the set point is 4.6 ± 5.8 min.

In Figs. 9 and 10, operation times and total amounts of blood loss, respectively, are shown with blood pressure control (13 cases) and without control (34 cases) in the operations for total pelvic exenteration, which were performed by the same surgeons. We compared the operation times and the amounts of blood loss in the operations for total pelvic exenteration, because a comparison of those from different operations is meaningless and because our system was applied to

Table 15. Averaged results of blood pressure control (28 cases).

T_s (min)	A_o (mmHg)	Duration (min)
15.1 ± 10.1	7.2 ± 3.6	43.9 ± 10.3

T_s: Settling time
A_o: Overshoot
Duration: Time per hour that the actual response is inside $\pm$ 10% of the target MAP

Table 16. Averages and standard deviations of operation times and blood loss during operations of total pelvic exenteration with blood pressure control (13 cases) and without blood pressure control (34 cases).

	Without BP control	With BP control
Operation time (h)	15.8 ± 4.0	11.5 ± 3.1 *
Blood loss (g)	8440 ± 4630	4880 ± 3390 **

*p<0.01

$^{**}p<0.05$

(p is the level of statistical reliability.)

operations for total pelvic exenteration the majority of times. In Table 16, the averages and standard deviations of operation times and the amounts of blood loss during operations of total pelvic exenteration with or without blood pressure control are shown. By Wilcoxon testing, the effects of blood pressure control on the operation time and on the blood loss were judged as "statistically significant at 5% level" [18].

6. DISCUSSION

Our blood pressure control system is an improvement upon the system developed in [13] for clinical application. The modifications are made mainly in four points:

- the model parameters of the response of the MAP to the hypotensive drug and the poles of the feedback control system
- auto-tuning method of the controller gain
- risk control algorithm
- identification of dose-response characteristics of each patient.

Various researches have been reported on the subject of the blood pressure control [1-12], but none of them were applied in clinical hypotensive anesthesia during surgical operation to the best of our knowledge. On the other hand, our system could maintain the patient's blood pressure accurately at the target level for hours without placing the patient in any danger. We think the major reasons which led our system to successful clinical applications are "use of the state-predictive servo mechanism for feedback control of MAP" and "introduction of the logical mechanism (i.e. inference rules and fuzzy-like logics) for risk control."

As for feedback control of MAP, any positive countermeasure was not taken to overcome the pure delay included in the dose response by the previous researches except [6, 9-11]. Actually, standard control mechanisms for delay-free plants such as PID controllers, ordinary adaptive controllers, LQ-type optimal controllers and rule-based controllers were used in [1-5, 7, 8]. Those controllers can attain a certain level of performance if the pure delay is small enough compared with the time-constant, but not if the delay is not small enough. Furthermore, no systematic method has been established to design those controllers for plants with a pure delay so that specified amounts of delay and gain margins are guaranteed. On the contrary, the state-predictive controller, which we use, can attain high performance even if the pure delay is large and a theoretical method is available to assure dead time and gain margins for the closed-loop system [14-16]. In [9] and [11], an adaptive controller and a self-tuning controller considering a pure delay of the plant is used respectively, but we cannot expect that they work well under such noisy conditions as those during surgical operations. In [6] and [10], the Smith controller and the model predictive controller (MPC), which are well-known as methods to overcome pure delay, are used, respectively. As for the MPC, the performance of the control system cannot be predicted easily, because the relation between parameters of the controller and the performance of the control system (e.g. poles of the control system, stability, etc.) remains unclear. Furthermore, a systematic method has not been established either to design an MPC controller for plants with a pure delay so that specified amounts of dead time and gain margins are guaranteed. Thus, the state-predictive controller is more appropriate than the MPC. Comparison of the Smith controller and the state-predictive controller is as follows. The Smith controller is derived by equivalent transformation of block diagrams and can overcome the difficulty caused by the pure delay as far as the closed-loop transfer function from the reference variable to the controlled variable is concerned. However, effects of disturbances are not taken into account in the equivalent transformation. As a result, the poles of the original plants remain unchanged in the closed-loop transfer functions from disturbances to the controlled variable. This implies that the Smith controller cannot stabilize unstable plants and faces difficulty in removing offsets for plants with integrators. On the other hand, the state-predictive controller is derived from the difference-differential equation describing the plant with pure delay and does not include the above difficulties. Namely, it moves the poles of the original plants completely to the new specified locations, and thus can stabilize unstable plants and remove offsets for plants with integrators.

As for the auto-tuning method of the controller gain, such a mechanism must be implemented to cope with dose-response characteristic variations with time. Model reference adaptive control (MRAC) and multiple model adaptive control (MMAC) are used for this purpose in [9] and in [10], respectively. Furthermore, adaptive predictive control, which can handle unknown and time-varying pure time delays, is proposed [23]. However, during surgical operation, very large disturbance and noise caused by short-time noxious stimulation, continuing stimulation of operative manipulation, the infusion of drugs (e.g. muscle relaxant), rapid bleeding, etc. add to the measured MAP. The peak-to-peak noise on the MAP is usually about 20 mmHg. In particular, the disturbance caused by continuing stimulation of operative manipulation occasionally makes the MAP about 10 mmHg higher than that without the stimulation for 5 min or longer. In such case, the essential change of the MAP cannot be measured accurately. Therefore, a rule-base auto-tuning method of the controller gain is adopted. This is determined by modifying the method in [13] so that

the infusion rate may decrease quickly enough when blood pressure decreases. In order to avoid the overinfusion, the maximal infusion rate of the hypotensive drug is set to 20 μg/kg/min. The safety, reliability and performance of our auto-tuning method were confirmed by experiments on dogs. Our system has worked well in all cases with no problems. However, because rapid decrease of the MAP caused by rapid bleeding or operative manipulation might happen during surgical operation, we should make an improvement in the auto-tuning method for extra safety.

As for risk control, no discussion may be necessary about its importance and necessity in clinical applications. The risk control algorithm plays an important role in maintaining the patient's blood pressure at a target level without placing the patient in any danger. The algorithm implemented in our system infers the patient's condition and takes appropriate actions according to the condition. To be concrete, it automatically stops infusion of the hypotensive drug when necessary, adjusts the infusion rates of the intravenous fluid, and issues messages to the anesthesiologists regarding treatments. This risk control algorithm is constructed based on the results of hearing investigation on the countermeasures during surgical operation. It makes decisions only for the ranges of the measurements determined by the anesthesiologists. When one of the measurements is out of range, the risk control algorithm displays that measurement with an alarm sound distinctive from others. In clinical applications, our risk control algorithm inferred patient's conditions appropriately and helped to maintain the patient's blood pressure accurately. For example, when blood pressure became much lower than the target level caused by rapid bleeding at about 5.2 hours in Fig. 7, our algorithm stopped infusion of the hypotensive drug and increased the infusion rates of the intravenous fluid, allowing the blood pressure to quickly return to the target level. Thus, it can reduce anesthesiologists' worry about risks accompanied with the blood pressure control. However, it works only when the measurements are within the ranges determined by the anesthesiologists as mentioned above. Also, it is incomplete and might be too simple because it does not take into account enough clinical parameters to judge all possible patient's conditions and because there are some problems in clinical conditions that cannot be judged from the measurements. Therefore, the present risk control algorithm cannot take the place of anesthesiologists and the final decisions of treatments except for stopping infusion of the hypotensive drug and adjusting the infusion rate of intravenous fluid must be made by anesthesiologists. We have to make improvements by adding some other clinical parameters and taking some other conditions of patients into account.

It should be noted that our system can work with other hypotensive drugs (e.g. sodium nitroprusside) only by changing the default parameter values and modifying the inference rules for stopping infusion of the hypotensive drug.

7. CONCLUSION

In order to maintain the blood pressure at a substantially low level during surgical operation, we have developed a blood pressure control system with a risk control algorithm. The risk control algorithm was developed based on interviews with anesthesiologists. Our system was applied to 28 patients and its efficiency was assured. As the result of the blood pressure control, the amounts of blood loss and operation time were considerably reduced.

At present, our system can be used only in Kyoto University Hospital, but a new system is being developed, which can be used in other hospitals.

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