Automated drug delivery system to control systemic arterial pressure, cardiac output, and left heart filling pressure in acute decompensated heart failure

Kazunori Uemura,1 Atsunori Kamiya,1 Ichiro Hidaka,1 Toru Kawada,1 Shuji Shimizu,1 Toshiaki Shishido,1 Makoto Yoshizawa,2 Masaru Sugimachi,1 and Kenji Sunagawa3

1Department of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, Suita; 2Research Division on Advanced Information Technology, Information Synergy Center, Tohoku University, Sendai; 3Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Science, Fukuoka, Japan

Submitted 22 September 2005; accepted in final form 17 December 2005

IN THE MANAGEMENT OF PATIENTS with acute decompensated heart failure by myocardial infarction or after cardiac surgical procedures, cardiovascular agents such as inotropes and/or vasodilators are commonly used to control systemic arterial pressure (AP), cardiac output (CO), and left heart filling pressure (2, 13, 20). Because responses to these agents vary between patients and within patient over time, strict monitoring of patient condition and frequent adjustments of drug infusion rates are usually required. This is a difficult and time-consuming process, especially in hemodynamically unstable patients. Several closed-loop systems to automate drug infusion have been developed to facilitate this process (10, 11, 18, 26, 27). Closed-loop control of AP with vasodilators was more precise and stable than manual controls (10, 11). Chitwood et al. (10) demonstrated that, compared with manual control, closed-loop control of postoperative hypertension significantly improves patient outcome by reducing the transfusion requirement and postoperative blood loss. Although closed-loop control of hemodynamics has been suggested to be useful in clinical settings, no closed-loop system so far developed is capable of controlling the overall hemodynamics; i.e., controlling AP, CO, and left heart filling pressure simultaneously (18). This is because all previous systems attempted to directly control the hemodynamic variable by estimating response of the variable to drug infusion (10, 11, 18, 26, 27). Although such an approach worked well in controlling a single variable, it cannot be applied to control of the three variables, because it is difficult to simultaneously estimate their responses to the infusions of multiple drugs.

In this study, we developed a new automated drug delivery system that is capable of controlling AP, CO, and left atrial pressure (Pla). We modeled the entire cardiovascular system by extending Guyton’s framework of circulatory equilibrium (16, 17, 24, 25). As shown in Fig. 1, the extended framework consists of an integrated cardiac output curve characterizing the pumping ability of the left and the right heart and a venous return surface characterizing the venous return property of the systemic and pulmonary circulation (24, 25). The intersection point of the integrated CO curve and the venous return surface predicts the equilibrium point of CO, Pla, and right atrial pressure (Pra) (Fig. 1) (24, 25). Once CO, Pla, and Pra are predicted from the intersection point, systemic arterial resistance determines AP. On the basis of this framework, instead of directly controlling AP, CO, and Pla, our system controls the integrated CO curve with dobutamine (Dob), the venous return surface with 10% dextran 40 (Dex) and furosemide (Fur), and systemic arterial resistance with sodium nitroprusside (SNP), thereby controlling the three hemodynamic variables.

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Address for reprint requests and other correspondence: K. Uemura, Dept. of Cardiovascular Dynamics, National Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita 565-8565, Japan (e-mail: kuemura@ri.ncvc.go.jp).
The purpose of this study was, therefore, to develop and validate the new automated drug delivery system. We evaluated the efficacy of our system in a canine model of acute ischemic heart failure. Our results indicated that this novel automated drug delivery system was able to control AP, CO, and Pla simultaneously with reasonably good accuracy and stability.

METHODS

Cardiac Output Curve, Venous Return Surface, and Arterial Resistance

On the basis of previous studies, we parameterized the integrated CO curve by the pumping ability of the left heart (SL), the venous return surface by total stressed blood volume (V), and the systemic arterial resistance by R (see APPENDIX A) (24, 25). Our system aims to control these cardiovascular parameters to achieve target AP (AP*), target CO (CO*), and target Pla (Pla*).

Automated Drug Delivery System

Figure 2A illustrates a block diagram of the automated drug delivery system, using a negative feedback mechanism. Target values of SL (SL*), V (V*), and R (R*) are determined according to the AP*, CO*, and Pla* (see APPENDIX B). The subject’s SL, V, and R are calculated from the measured AP, CO, Pla, and Pra (Fig. 2A). SL, V, and R are compared with SL*, V*, and R*, respectively.

To minimize the difference between SL* and SL (∆SL = SL* − SL) and the difference between R* and R (∆R = R* − R), proportional-integral (PI) feedback controllers adjust infusion rates of Dob and SNP, respectively (Fig. 2A). In the PI controller (Fig. 2B), ∆SL (or ∆R) and the difference integrated with an integral gain (Ki) are summed and scaled by a proportional gain (Kp) to give the infusion rate of Dob (or SNP). We determined values of Ki and Kp on the

![Diagram of circulatory equilibrium for cardiac output (CO), venous return (COV), left atrial pressure (Pla), and right atrial pressure (Pra). The equilibrium CO, Pla, and Pra are obtained as the intersection point of the venous return surface and integrated cardiac output curve. [Modified from Uemura et al. (Ref 25).]](http://jap.physiology.org/issue/100/4/1279/Fig1.png)
basis of open-loop response of $S_l$ (or R) to the infusion of Dob (or SNP) (4, 9).

To minimize the difference between $V^{*}$ and $V$ ($\Delta V = V^{*} - V$), a nonlinear (NL) feedback controller (Fig. 2A) adjusts the infusion of Dex or injection of Fur on the basis of the following “if-then” rules:

Rule 1: If $\Delta V \geq X_1 \text{ml/kg}$ then infuse Dex ($Y_1$, $\text{ml/min}$)

Rule 2: If $\Delta V \leq X_2 \text{ml/kg}$ then inject Fur ($Y_2$, mg)

We determined values of $X_1$, $Y_1$, $X_2$, and $Y_2$ on the basis of the open-loop response of $V$ to the infusion of Dex and Fur.

These adjustment processes are repeated in parallel and continued until the differences disappear.

Preparation

We used 35 adult mongrel dogs in this study [both sexes, body weight 25 kg (SD 4)]. Care of the animals was in strict accordance with the guiding principles of the Physiological Society of Japan. All protocols were approved by the Animal Subjects Committee of the National Cardiovascular Center. Anesthesia was induced with pentobarbital sodium (25 mg/kg). Animals were intubated endotracheally. Isoflurane (1.0%) was inhaled continuously to maintain an appropriate level of anesthesia during the experiment. A catheter (8-Fr) was placed in the right femoral artery, which was connected to a pressure transducer (DX-200, Nihon Kohden, Tokyo, Japan) to measure AP. After a median sternotomy, a small pericardial incision was made at the level of the aortic root. Through the incision, an ultrasonic flow meter (20A594, Transonics, Ithaca, NY) was placed around the ascending aorta to measure CO. Fluid-filled catheters were placed in the right external jugular vein, from which Fur was injected after a latency of 10 s. A catheter (6-Fr) was placed in the right femoral vein. A roller pump (Minipuls 3, Gilson, Middleton, WI) was attached to the venous line to infuse Dex. A double-lumen catheter was also introduced into the right femoral vein for administration of Dob and SNP. Infusion pumps (CFV-3200, Nihon Kohden) were used for Dob and SNP infusion. The infusion rates of Dex, Dob, and SNP were controlled with a personal computer (MA20V, NEC, Tokyo, Japan) through a 12-bit digital-to-analog converter (DA12-8PCI, Contec, Osaka, Japan). A catheter (6-Fr) was placed in the right external jugular vein, from which Fur was injected after a command signal from the computer.

Experimental Protocols

We induced left ventricular failure (LVF) in all the animals by embolizing the left circumflex coronary artery with glass microspheres (90 \mu m in diameter) (24, 25). We adjusted the amount of injected microspheres to increase Pla to more than 18 mmHg or decrease CO to less than 70 ml/min kg⁻¹. When ventricular tachycardia or frequent premature ventricular contractions were noted, lidocaine (1 mg/min) was infused to suppress the arrhythmia.

Response of cardiovascular parameters to drug infusion. Under open-loop conditions, we examined the response of cardiovascular parameters to drug infusions in 21 dogs with LVF. In 10 dogs, we infused Dob in a stepwise manner at 6 \mu g kg⁻¹ min⁻¹ for 10 min to obtain a step response of $S_l$. In six dogs, we infused SNP at 2 \mu g kg⁻¹ min⁻¹ for 10 min to obtain a step response of $R$. In five dogs, we infused Dex at 0.4 ml/min kg⁻¹ for 10 min to observe the response of $V$. In seven dogs, we injected Fur (20 mg, bolus iv) and observed the response of $V$ and urine volume for 50 min.

Application of the automated drug delivery system. We applied the system to the other 14 dogs with LVF. We first defined $AP^*$ (90–105 mmHg), $CO^*$ (90–100 ml min⁻¹ kg⁻¹), and $Pla^*$ (8–12 mmHg), which were fed into the system to determine $S_l^*$, $V^*$, and $R^*$ (see APPENDIX II). The controllers were then activated by closing the loops. In 12 dogs (group 1), we observed the performance of the system over 50–60 min. In two dogs (group 2), we observed the performance of the system over 100–150 min to evaluate stability of the closed-loop control over a longer periods of time.

With the use of the computer, analog signals of AP, CO, Pla, and Pra were digitized at 200 Hz with a 12-bit analog-to-digital converter [AD12-16U(PCIE), Contec, Osaka, Japan] and stored on a hard disk for offline analysis. In the closed-loop control, the digitized signals were smoothed by a low-pass filter (time constant, 10 s) and were used as the system controlled variables. The infusion rates of Dob, SNP, and Dex were also stored. Urine volume after the injection of Fur was recorded.

Data Analysis

Evaluation of the response of cardiovascular parameters and design of the controller. We described the step response of $S_l$ and $R$ by a transfer function of a first-order model with a transport delay. In this model, change in $S_l$ from baseline ($\delta S_l$) in response to Dob infusion can be expressed by the following formula:

$$\delta S_l(t) = \begin{cases} 1 - \exp\left(-\frac{t-L}{T}\right) & (t \geq L) \\ 0 & (t < L) \end{cases}$$

where $G$ is static gain [ml/min kg⁻¹ kg⁻¹ (umg⁻¹ kg⁻¹ min⁻¹)], $L$ is transport delay (s), and $T$ is time constant (s). Change in $R$ from baseline ($\delta R$) in response to the SNP infusion can be expressed similarly and is characterized by $G$ [mmHg ml/min kg⁻¹ kg⁻¹ (umg⁻¹ kg⁻¹ min⁻¹)], $L$ (s), and $T$ (s). We estimated the parameters of the transfer function by approximating $\delta S_l$ and $\delta R$ to Eq. 1 using the least square method. We averaged the parameters of the transfer function of $S_l$ response for 10 animals and those of $R$ response for 6 animals. The averaged parameters were used to determine the PI gain constants, $K_i$ and $K_p$, in accordance with the method of Chien et al. (9). Their method provides PI constants that permit the regulated variable to respond rapidly without overshoot (4, 9).

We evaluated the change in $V$ from baseline ($\delta V$) in response to the infusion of Dex and Fur. On the basis of $\delta V$, we determined the constants ($X_1$, $Y_1$, $X_2$, and $Y_2$) of the if-then rules.

Efficacy of the automated drug delivery system. We calculated the following indexes to evaluate the accuracy and stability of the control of AP, CO, and Pla by the new system: the time required for the hemorrhagic variables to reach the acceptable ranges of the target values (±10 mmHg for AP, ±10 ml/min kg⁻¹ for CO, ±2 mmHg for Pla), and the standard deviations of the steady-state differences between AP and AP*, between CO and CO*, and between Pla and Pla*. Because steady states were reached within 30 min in all the variables in the present study, standard deviations were calculated from 30 min after the loop was closed.

Statistics

Group data are expressed as means (SD) unless otherwise stated. Student's paired t-test was used to compare hemodynamic data at baseline and after the coronary embolization. One-way ANOVA with Tukey’s post hoc test was used to compare hemodynamic data before, during, and after the closed-loop control of hemodynamics. The level of statistical significance was defined as $P < 0.05$.

RESULTS

Hemodynamic data at baseline and after left circumflex coronary artery embolization are summarized in Table 1. Coronary embolization more than doubled Pla [from 7.5 (SD 1.9) to 19.4 (SD 6.2) mmHg] and halved CO [from 131.4 (SD 7.0) to 79.7 (SD 7.0) ml/min kg⁻¹].
Table 1. Hemodynamic data at baseline and after left circumflex coronary artery embolization

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Embolization</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>141.3 (19.5)</td>
<td>146.2 (28.8)</td>
</tr>
<tr>
<td></td>
<td>[112.0–188.3]</td>
<td>[81.4–197.9]</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>109.1 (18.7)</td>
<td>90.9 (16.5)</td>
</tr>
<tr>
<td></td>
<td>[76.4–140.0]</td>
<td>[66.9–135.6]</td>
</tr>
<tr>
<td>CO, ml·min⁻¹·kg⁻¹</td>
<td>131.4 (40.9)</td>
<td>66.8 (23.3)</td>
</tr>
<tr>
<td></td>
<td>[64.5–229.2]</td>
<td>[30.3–121.7]</td>
</tr>
<tr>
<td>PLa, mmHg</td>
<td>7.5 (1.9)</td>
<td>19.4 (6.2)</td>
</tr>
<tr>
<td></td>
<td>[4.7–12.8]</td>
<td>[7.9–34.5]</td>
</tr>
<tr>
<td>Pra, mmHg</td>
<td>4.2 (1.2)</td>
<td>6.0 (1.8)</td>
</tr>
<tr>
<td></td>
<td>[2.1–7.2]</td>
<td>[3.5–9.9]</td>
</tr>
<tr>
<td>S,L, ml·min⁻¹·kg⁻¹</td>
<td>54.3 (18.1)</td>
<td>19.1 (7.6)</td>
</tr>
<tr>
<td></td>
<td>[25.2–105.9]</td>
<td>[8.0–33.7]</td>
</tr>
<tr>
<td>V, ml/kg</td>
<td>31.0 (6.6)</td>
<td>32.3 (4.9)</td>
</tr>
<tr>
<td></td>
<td>[21.7–45.2]</td>
<td>[20.6–43.7]</td>
</tr>
</tbody>
</table>

Values are means (SD) (n = 35 in each group). Numbers in brackets are the ranges. HR, heart rate. AP, systemic arterial pressure; CO, cardiac output; Pla, left atrial pressure; Pra, right atrial pressure; S,L, pumping ability of the left heart; R, systemic arterial resistance; V, stressed blood volume. *P < 0.01 vs. baseline.

40.9) to 66.8 (SD 23.3) ml·min⁻¹·kg⁻¹. This decreased S,L to about one-third of the baseline value, which indicates substantial downward shift of the left cardiac output curve. These changes are compatible with severe LVF.

Response of Cardiovascular Parameters to Drug Infusion

Figure 3 shows the open-loop responses of cardiovascular parameters to drug infusions. Figure 3, A and B, shows the averaged time course of δS,L during Dob infusion (n = 10) and that of δR during SNP infusion (n = 6), respectively. Dob infusion increased δS,L, and SNP infusion decreased δR exponentially. The results of the fit of δS,L and δR to Eq. 1 are summarized in Table 2. The fact that the correlation coefficients were close to unity, with a small standard error of the estimate relative to the amount of δS,L and δR, suggested that the approximation of δS,L and δR to Eq. 1 was reasonably accurate. On the basis of the averaged parameters of the transfer function (Table 2), we determined the PI gain constants for Dob infusion [K_i = 0.01 s⁻¹, K_p = 0.06 μg·kg⁻¹·min⁻¹·(ml·min⁻¹·kg⁻¹)⁻¹] and for SNP infusion [K_i = 0.007 s⁻¹, K_p = −1.37 μg·kg⁻¹·min⁻¹·(mmHg·min·ml⁻¹·kg⁻¹)⁻¹].

Figure 3C shows the averaged time course of δV in response to Dex infusion (n = 5). δV increased and plateaued [7.2 ml/kg (SD 2.2)] after the cessation of Dex infusion. δV at the plateau was greater than the total volume of Dex infused (4 ml/kg), suggesting transvascular fluid absorption by colloid osmotic pressure (3). Figure 3D shows the averaged time course of δV after a single intravenous injection of Fur (20 mg, n = 7). δV gradually decreased and reached a trough [−4.3 ml/kg (SD 3.5)] around 30 min after the Fur injection. Average urine volume was 180 ml (SD 94). On the basis of these responses, we determined the constants of the if-then rules as

\[
\delta R = \frac{K_i}{K_p} \cdot \delta V
\]

Fig. 3. Response of cardiovascular parameter to drug infusion. A: averaged response of S,L to stepwise Dob infusion (6 μg·kg⁻¹·min⁻¹) (n = 10). The ordinate indicates change in S,L from baseline (δS,L). B: averaged response of R to stepwise SNP infusion (2 μg·kg⁻¹·min⁻¹) (n = 6). The ordinate indicates change in R from baseline (δR). C and D: averaged response of V to Dex infusion (0.4 ml·min⁻¹·kg⁻¹) (C, n = 5) and to Fur (20 mg) injection (D, n = 7). The ordinates indicate change in V from baseline (δV). Data are expressed by mean (solid line) ± SD (broken line).
mia and hypervolemia (hence infusion of Dex and injection of Fur), we introduced a dead zone (–2 ml/kg < ΔV < 1 ml/kg) into the rules (4). We set continuous checking for rule 1 and checking at 20-min intervals for rule 2.

With the controllers thus designed, we evaluated the performance of the automated system in the next protocol.

**Performance of the Automated Drug Delivery System**

Figure 4 shows the experimental trial in a representative case. The automated system was activated at 0 min. Figure 4A shows the time courses of the infusion rates of Dob and SNP and the accumulated volume of infused Dex. In this case, Fur was not injected. Figure 4B shows the time courses of SL, R, and V. Infusion rates of Dob, SNP, and Dex were adjusted so that SL, R, and V reached their respective target values. By controlling the cardiovascular parameters, the automated system controlled AP, CO, and Pla accurately and stably as demonstrated in Fig. 4C. AP, CO, and Pla reached their respective target levels within 30 min and remained at these levels.

Figure 5 summarizes the results obtained for 12 dogs (group 1), demonstrating the effectiveness of the performance of the automated system. Figure 5A shows averaged time courses of the infusion rates of Dob and SNP, and the accumulated volume of infused Dex. The average infusion rates of Dob and SNP were 4.7 μg·kg⁻¹·min⁻¹ (SD 2.6) and 4.2 μg·kg⁻¹·min⁻¹ (SD 1.8), respectively. The average volume of infused Dex was 2.4 ml/kg (SD 1.9). Fur was injected once in one animal and twice in another animal. In these two animals, V decreased by 3.8–10.2 ml/kg in response to the injection of Fur with a total urine volume of 250–300 ml. Figure 5B shows averaged time courses of difference between SL and SL° (SL – SL°), difference between R and R° (R – R°), and difference between V and V° (V – V°). Once the system was activated, these differences rapidly converged to the zero lines in all the animals. SL was restored to subnormal conditions [33.0 ml·min⁻¹·kg⁻¹ (SD 2.6)] irrespective of the magnitude of depression before the control [13.8 ml·min⁻¹·kg⁻¹ (SD 3.5), from 9.4 to 20.5 ml·min⁻¹·kg⁻¹]. These resulted in accurate and stable control of AP, CO, and Pla (Fig. 5C). The ordinates of Fig. 5C indicate the difference between AP and AP° (AP – AP°), difference between CO and CO° (CO – CO°), and difference between Pla and Pla° (Pla – Pla°). These differences also converged to the zero lines rapidly. The average times for AP, CO, and Pla to reach the acceptable ranges were 5.2 min (SD 6.6), 6.8 min (SD 4.6), and 11.7 min (SD 9.8),

<table>
<thead>
<tr>
<th>SL*</th>
<th>L</th>
<th>T</th>
<th>r</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.6 (2.7)</td>
<td>63.5 (46.9)</td>
<td>79.0 (78.0)</td>
<td>0.91 (0.09)</td>
<td>2.0 (0.7)</td>
</tr>
<tr>
<td>–0.21 (0.08)</td>
<td>69.8 (26.1)</td>
<td>117.1 (80.2)</td>
<td>0.93 (0.02)</td>
<td>0.06 (0.02)</td>
</tr>
</tbody>
</table>

Values are means (SD). δSL*, change in SL from baseline; δR*, change in R from baseline; G, static gain of δs [ml·min⁻¹·kg⁻¹ (μg·kg⁻¹·min⁻¹)⁻¹] and of δR [mmHg·min⁻¹·kg⁻¹ (μg·kg⁻¹·min⁻¹)⁻¹]; L, transport delay (s); T, time constant (s); r, correlation coefficient; SEE, standard error of the estimate of δs and δR (ml·min⁻¹·kg⁻¹) and of δR (mmHg·min⁻¹·kg⁻¹).
respectively. The average standard deviations from the target values were small for AP [4.4 mmHg (SD 2.6)], CO [5.4 ml·min⁻¹·kg⁻¹ (SD 2.4)] and Pla [0.8 mmHg (SD 0.6)]. In case of severe hypotension, restoring normal AP should be done within a few minutes to prevent cerebral ischemia. Four of 12 dogs exhibited severe hypotension [AP, 67 mmHg (SD 6)]. In these animals, AP* [95 mmHg (SD 4)] was attained within 4 min [mean 2.8 min (SD 0.7)]. Hemodynamic data before, during, and after the closed-loop control of hemodynamics are summarized in Table 3. After the system was turned off, AP, CO, and Pla gradually returned to their precontrol levels in 11 animals. In one animal, however, progressive hypotension followed by intractable ventricular fibrillation occurred –3 min after the system was turned off.

In two dogs (group 2), AP, CO, and Pla were controlled with reasonable stability over a longer periods of time (100–150 min). Standard deviations from target values were small for AP (3.9–7.8 mmHg), CO (2.7–6.6 ml·min⁻¹·kg⁻¹), and Pla (0.7–2.5 mmHg).

### Table 3. Hemodynamic data before, during, and after the closed-loop control of hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Before (n = 12)</th>
<th>During (n = 12)</th>
<th>After (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/mm</td>
<td>147.4 (26.8)</td>
<td>149.4 (25.0)</td>
<td>135.7 (25.2)†‡</td>
</tr>
<tr>
<td>AP, mmHg</td>
<td>86.7 (22.4)</td>
<td>97.0 (7.4)</td>
<td>75.2 (21.1)‡</td>
</tr>
<tr>
<td>CO, ml·min⁻¹·kg⁻¹</td>
<td>53.7 (14.6)</td>
<td>96.7 (5.3)†</td>
<td>53.5 (8.6)‡</td>
</tr>
<tr>
<td>Pla, mmHg</td>
<td>21.8 (5.5)</td>
<td>10.8 (1.2)†</td>
<td>18.5 (3.4)‡</td>
</tr>
<tr>
<td>Pra, mmHg</td>
<td>6.9 (1.8)</td>
<td>4.4 (0.9)†</td>
<td>7.4 (2.2)‡</td>
</tr>
<tr>
<td>SL, ml·min⁻¹·kg⁻¹</td>
<td>14.3 (4.0)</td>
<td>32.7 (2.6)†</td>
<td>15.1 (2.9)‡</td>
</tr>
<tr>
<td>R, mmHg/min·ml⁻¹·kg</td>
<td>1.5 (0.3)</td>
<td>1.0 (0.1)†</td>
<td>1.3 (0.4)‡</td>
</tr>
<tr>
<td>V, ml/kg</td>
<td>34.2 (4.9)</td>
<td>28.5 (2.3)†</td>
<td>34.0 (5.8)‡</td>
</tr>
</tbody>
</table>

Values are means (SD). *P < 0.05, †P < 0.01 vs. Before; ‡P < 0.01 vs. During.

### DISCUSSION

To the best of our knowledge, the automated drug delivery system we have developed is the first to successfully control AP, CO, and Pla simultaneously with reasonably good accuracy and stability. In a canine model of acute heart failure, our system automatically normalizes AP, CO, and Pla and maintains the levels stably within the desired ranges. Therefore, our system is potentially useful in the management of patients with acute decompensated heart failure.

### Previous Closed-Loop Systems Controlling Hemodynamic Variables

Several previous systems have attempted to control two hemodynamic variables simultaneously (18, 26, 27). However, it is difficult to expand them to closed-loop control of the overall hemodynamics.

Voss et al. (26) and Yu et al. (27) reported closed-loop systems to control AP and CO using inotropes and vasodilators in dogs. In these systems, all possible input-output relations between drug infusion and the response of the controlled variable have to be estimated; namely, inotrope-AP, inotrope-CO, vasodilator-AP, and vasodilator-CO relations. The reason for this is that these drugs affect AP and CO simultaneously to almost the same degree. If this approach is applied to simultaneous control of AP, CO, and Pla, at least nine input-output relations have to be estimated, because at least three drugs are required to independently control the three variables. This would make the system extremely complicated and therefore be practically unfeasible.

In addition, the input-output relations must be estimated online in individual animals to tune the drug controllers. The reason for this is that the relations differ widely between animals and within animal over time. Even the direction of the
output response can change. For example, CO usually increases in response to SNP infusion in subjects with failing hearts but may also decrease in subjects with preserved cardiac function (23, 26). In the closed-loop system of Voss et al., such estimation induced unacceptably large fluctuations in AP (26). The feasibility of such online estimation is questionable when drug infusion rates are allowed to vary simultaneously because of the difficulty to differentiate between drug effects. To avoid this problem, Hoeksel et al. (18) allowed only one drug to be varied at a time, whereas other drugs were kept constant in closed-loop control of AP and pulmonary arterial pressure during cardiac surgery. However, their adjustments of volume supplementation or dobutamine infusion were manual. Their system did not completely automate the control of hemodynamics.

Characteristics of Our System

Our system controls the cardiovascular parameters characterizing the integrated CO curve, venous return surface, and arterial resistance and as a result achieves target values for hemodynamic variables. Compared with previous systems, our system may appear to adopt a rather roundabout approach. Our concept is that controlling the cardiovascular parameters is physiologically more rational, because it is equivalent to directly controlling the mechanical determinants of circulation. As indicated by Guyton et al. (16, 17), when the mechanics of the circulation are considered, the hemodynamic variables such as AP, CO, and atrial pressures are the effects, or dependent variables. Blood volume and the mechanical properties of the heart and vasculature, such as heart rate, ventricular contractility, and vascular resistance, are the causes, or independent variables. The integrated CO curve and venous return surface display these properties through the relationship between the flow and atrial pressures (24, 25). The total artificial heart control system developed by Abe et al. (1) adjusted its output response can change. For example, CO usually increases in response to SNP infusion in subjects with failing hearts but may also decrease in subjects with preserved cardiac function (23, 26). In the closed-loop system of Voss et al., such estimation induced unacceptably large fluctuations in AP (26). The feasibility of such online estimation is questionable when drug infusion rates are allowed to vary simultaneously because of the difficulty to differentiate between drug effects. To avoid this problem, Hoeksel et al. (18) allowed only one drug to be varied at a time, whereas other drugs were kept constant in closed-loop control of AP and pulmonary arterial pressure during cardiac surgery. However, their adjustments of volume supplementation or dobutamine infusion were manual. Their system did not completely automate the control of hemodynamics.

Characteristics of Our System

Our system controls the cardiovascular parameters characterizing the integrated CO curve, venous return surface, and arterial resistance and as a result achieves target values for hemodynamic variables. Compared with previous systems, our system may appear to adopt a rather roundabout approach. Our concept is that controlling the cardiovascular parameters is physiologically more rational, because it is equivalent to directly controlling the mechanical determinants of circulation. As indicated by Guyton et al. (16, 17), when the mechanics of the circulation are considered, the hemodynamic variables such as AP, CO, and atrial pressures are the effects, or dependent variables. Blood volume and the mechanical properties of the heart and vasculature, such as heart rate, ventricular contractility, and vascular resistance, are the causes, or independent variables. The integrated CO curve and venous return surface display these properties through the relationship between the flow and atrial pressures (24, 25). The total artificial heart control system developed by Abe et al. (1) adjusted its output response can change. For example, CO usually increases in response to SNP infusion in subjects with failing hearts but may also decrease in subjects with preserved cardiac function (23, 26). In the closed-loop system of Voss et al., such estimation induced unacceptably large fluctuations in AP (26). The feasibility of such online estimation is questionable when drug infusion rates are allowed to vary simultaneously because of the difficulty to differentiate between drug effects. To avoid this problem, Hoeksel et al. (18) allowed only one drug to be varied at a time, whereas other drugs were kept constant in closed-loop control of AP and pulmonary arterial pressure during cardiac surgery. However, their adjustments of volume supplementation or dobutamine infusion were manual. Their system did not completely automate the control of hemodynamics.

Clinical Application of Our System

Our system will reduce the stress and work imposed on physicians and nurses who are managing patients with unstable hemodynamic conditions. These personnel will be able to spend more time on other patient-related activities, thereby improving the quality of patient care (10, 11). We believe that the closed-loop control of overall hemodynamics can extend the improvement in postoperative outcome demonstrated by Chitwood et al. (10) to various aspects of clinical cardiology or cardiac surgery.

In clinical settings, multisystem disorders such as renal disease, anemia, and diabetes may affect the performance of our system. Renal disease can weaken the response of V to the infusion of Fur. The hemodynamic changes in anemia include increased preload and reduced arterial resistance as compensatory mechanisms for the reduced oxygen-carrying capacity of the blood (8). These changes may affect the control of V and R by our system. In patients with diabetic cardiomyopathy, the sensitivity of S1 to Dob infusion may be reduced (5). Drugs prescribed before hospitalization such as β-blockers, or used during hospitalization such as morphine may also affect the performance of our system. Chronic β-adrenergic blockade can weaken the sensitivity of S1 to Dob infusion (2). Administration of morphine may change the response of V and R to the drugs infused (15). We must clarify these effects on the performance of our system as thoroughly as possible before our system can be considered for clinical application.

In the routine clinical environment, CO, and pulmonary artery occlusion pressure, a substitute for Pla, are measured intermittently with a Swan-Ganz catheter. For clinical application of our system, it is a prerequisite to monitor these variables continuously. Several methods have been developed to continuously monitor CO or the pulmonary artery occlusion pressure (6, 12). Integrating these methods into our system would bring the clinical application of our system closer to reality.

Limitations

All the experiments of this study were conducted in anesthetized, open-chest dogs. Anesthesia and surgical trauma affect the cardiovascular system significantly. Whether the present system is efficacious in conscious, closed-chest animals (including humans) remains to be seen.

We parameterized the integrated cardiac output curve and the venous return surface using Eqs. A1, A2, and A4 (24, 25). Even if the actual curve or surface deviate slightly from those
estimated by these equations, our system compensates such deviations by the negative feedback mechanism. However, we did not confirm whether the estimation works well outside the physiological ranges of Pla and Pra, particularly under low atrial pressures (24, 25). The efficacy of our system in such conditions remains to be evaluated.

Our system controls R with vasodilators only and lacks a controller to increase R with vasoconstrictors. This will not be a major problem because the pathophysiology of acute heart failure is characterized by excessive vasoconstriction due to enhanced activity of sympathetic and renin-angiotensin systems (19). Vasoconstrictor control is necessary, however, for the management of patients with excessive vasodilatation, such as those in septic shock (21).

In this study, control of SL was accurate and stable. However, it would be impossible to restore SL pharmacologically if SL is more severely depressed than those seen in this study as in the case of more diffuse myocardial disease or superimposed coronary artery disease. We must clarify in future studies to what magnitude of SL depression can our system restore it reliably. In addition, how to use our system with mechanical circulatory support such as the intra-aortic balloon pump in case of the severe SL depression remains to be established.

In the present design, if SL is unable to respond to the infusion of Dob, the system will automatically increase the infusion rate of Dob owing to its negative feedback mechanism. This would be problematic especially in case of arrhythmia, which is a serious noise in the closed-loop control of SL. If not appropriately suppressed, frequent premature ventricular contractions or ventricular tachycardia will depress SL owing to disorganized ventricular contraction. In response to the depressed SL, the system automatically increases the infusion rate of dobutamine. This could further exacerbate the arrhythmia, thus leading to a vicious cycle and collapse of the hemodynamics. To prevent such malfunction, a smart “sensor” that will filter these unwanted artifacts should be included in our system.

In the present study, we recorded only the urine volume. Measurement of urine flow and sodium excretion is essential to evaluate renal function, which is a very important prognostic indicator in patients with acute decompensated heart failure (14). It would be desirable to add the monitoring of these parameters to our system to improve the quality of patient care.

In conclusion, by directly controlling the mechanical determinants of circulation, our automated drug delivery system allows simultaneous control of AP, CO, and Pla with reasonable accuracy and stability and is potentially a powerful clinical tool for the management of patients with acute decompensated heart failure.

APPENDIX A

Parameters of Integrated Cardiac Output Curve, Venous Return Surface, and Arterial Resistance

We parameterized the integrated CO curve, the venous return surface and the systemic arterial resistance on the basis of previous studies (24, 25). In the integrated CO curve, CO (ml·min⁻¹·kg⁻¹) is closely related to Pla (mmHg) by the following formula (24):

\[ CO = S_L \times \ln(\text{Pla} - 2.03) + 0.80 \]  

(A1)

and CO to Pra (mmHg) as follows:

\[ S_L = \frac{\text{CO}}{\ln(\text{Pla} - 2.03) + 0.80} \]  

(A3)

The venous return surface can be mathematically expressed by the following formula (25):

\[ V = \frac{V_\text{COV}}{0.129 - 19.61 \text{Pra} + 3.49 \text{Pla}} \]  

(A4)

V (ml/kg) is total stressed blood volume, and COV (ml·min⁻¹·kg⁻¹) is integrated venous return from systemic and pulmonary circulations. This relationship is also consistent among different animals (25). We used V to parameterize the venous return surface. V can be calculated from CO (= COV), Pla, and Pra by rewriting Eq. A4 as follows:

\[ V = (\text{CO} + 19.61 \text{Pra} + 3.49 \text{Pla}) \times 0.129 \]  

(A5)

We parameterized the systemic arterial resistance (R) (mmHg·ml⁻¹·min·kg⁻¹) by the following formula:

\[ R = \frac{(\text{AP} - \text{Pra}) \times \text{CO}}{0.88} \]  

(A6)

APPENDIX B

Determination of Target Parameters

On the basis of AP*, CO*, and Pla*, our system determines SL*, V*, and R* as follows: SL* is calculated by substituting CO* and Pla* into Eq. A3. By substituting baseline CO, Pla, and Pra into Eqs. A1 and A2, baseline SL and SR are calculated to determine α. SR (SR*) corresponding to SL* is predicted as:

\[ S_R = \alpha \cdot S_L^* \]  

(B1)

From Eq. A2 and B1, target Pra (Pra*) is predicted as:

\[ \text{Pra}^* = \exp((\text{CO}^*)(S_L^*) - 0.88) + 1.0 \]  

(B2)

By substituting CO*, Pla*, and Pra* into Eq. A5, V* can be determined. By substituting AP*, CO*, and Pra* into Eq. A6, R* can be calculated.

GRANTS

This study was supported by Grant-in-Aid for Young Scientists (B) (16700379) from the Ministry of Education, Culture, Sports, Science and Technology, by Health and Labour Sciences Research Grants for Research on Medical Devices for Analyzing, Supporting and Substituting the Function of the Heart, Kidney, and Blood Vessels (1285) from the Ministry of Health, Labour and Welfare of Japan, and by the Program for Promotion of Fundamental Studies in Health Science of the National Institute of Biomedical Innovation. This study was also conducted as a part of “Ground-based Research Announcement for Space Utilization” promoted by Japan Space Forum.

REFERENCES

1286 CLOSED-LOOP CONTROL OF HEMODYNAMICS