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

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Uemura, Kazunori, Atsunori Kamiya, Ichiro Hidaka, Toru Kawada, Shuji Shimizu, Toshiaki Shishido, Makoto Yoshizawa, Masaru Sugimachi, and Kenji Sunagawa. Automated drug delivery system to control systemic arterial pressure, cardiac output, and left heart filling pressure in acute decompensated heart failure. J Appl Physiol 100: 1278–1286, 2006. First published December 22, 2005; doi:10.1152/japplphysiol.01206.2005.—Pharmacological support with inotropes and vasodilators to control decompensated hemodynamics requires strict monitoring of patient condition and frequent adjustments of drug infusion rates, which is difficult and time-consuming, especially in hemodynamically unstable patients. To overcome this difficulty, we have developed a novel automated drug delivery system for simultaneous control of systemic arterial pressure (AP), cardiac output (CO), and left atrial pressure (Pla). Previous systems attempted to directly control AP and CO by estimating their responses to drug infusions. This approach is inapplicable because of the difficulties to estimate simultaneous AP, CO, and Pla responses to the infusion of multiple drugs. The circulatory equilibrium framework developed previously (Uemura K, Sugimachi M, Kawada T, Kamiya A, Jin Y, Kashihara K, and Sunagawa K. Am J Physiol Heart Circ Physiol 286: H2376–H2385, 2004) indicates that AP, CO, and Pla are determined by an equilibrium of the pumping ability of the left heart (Si), stressed blood volume (V), and systemic arterial resistance (R). Our system directly controls Si with dobutamine, V with dextran/furosemide, and R with nitroprusside, thereby controlling the three variables. We evaluated the efficacy of our system in 12 anesthetized dogs with acute decompensated heart failure. Once activated, the system restored Si, V, and R within 30 min, resulting in the restoration of normal AP, CO, and Pla. Steady-state deviations from 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 conclusion, by directly controlling the mechanical determinants of circulation, our system has enabled simultaneous control of AP, CO, and Pla with good accuracy and stability.

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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 $SL^*$, $V^*$, and $R^*$ 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 $SL$ ($\frac{SL - SL^*}{SL}$) and the difference between $R^*$ and $R$ ($\frac{R - R^*}{R}$), proportional-integral (PI) feedback controllers adjust infusion rates of Dob and SNP, respectively (Fig. 2A). In the PI controller (Fig. 2B), $\Delta SL$ (or $\Delta R$) 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

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**Fig. 1.** 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).]

**Fig. 2.** A: block diagram of an automated drug delivery system for simultaneous control of systemic arterial pressure (AP), CO, and Pla. AP*, CO*, and Pla* represent target AP, target CO, and target Pla, respectively. From these target variables, target values of pumping ability of the left heart ($SL^*$), stressed blood volume ($V^*$), and systemic arterial resistance ($R^*$) are determined. Subject’s $SL$, $V$, and $R$ are calculated from measured AP, CO, Pla, and Pra. Proportional-integral (PI) controllers adjust infusion rate of dobutamine (Dob) and sodium nitroprusside (SNP) to minimize the difference between $SL^*$ and $SL$ ($\frac{SL - SL^*}{SL}$) and the difference between $R^*$ and $R$ ($\frac{R - R^*}{R}$), respectively. Nonlinear (N-L) controller adjusts infusion of 10% dextran 40 (Dex) or injection of furosemide (Fur) so that the difference between $V$ and $V^*$ is minimized. B: block diagram of the PI controller. $Ki$ and $Kp$ represent the integral and proportional gain constants, respectively; $s$ is a Laplace operator.

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basis of open-loop response of SL (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 \( \Delta V \geq \Delta V_1 \), infused Dex (\( Y_1, \text{ml/min} \))

Rule 2: If \( \Delta V \leq \Delta V_2 \), inject Fur (\( Y_2, \text{mg} \))

We determined values of \( \Delta V_1, Y_1, \Delta V_2, \text{and } Y_2 \) 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 inserted to measure urine volume.

A urinary catheter and the damping ratio of the fluid filled catheters for the pressure measurements were 21 Hz and 0.22, respectively. A urinary catheter was inserted to measure urine volume.

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 (CVF-3200, Nihon Kohden, Tokyo, Japan) 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\( \cdot \)min\(^{-1}\)\( \cdot \)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\( \cdot \)kg\(^{-1}\)\( \cdot \)min\(^{-1}\) for 10 min to obtain a step response of SL. In six dogs, we infused SNP at 2 \( \mu \)g\( \cdot \)kg\(^{-1}\)\( \cdot \)min\(^{-1}\) for 10 min to obtain a step response of R. In five dogs, we infused Dex at 0.4 ml\( \cdot \)min\(^{-1}\)\( \cdot \)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\( \cdot \)min\(^{-1}\)\( \cdot \)kg\(^{-1}\)), and Pla* (8–12 mmHg), which were fed into the system to determine SI*, 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 Pla were digitized at 200 Hz with a 12-bit analog-to-digital converter [AD12-16U(PC)E, 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**

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**Data Analysis**

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

\[
\delta S_I(t) = \begin{cases} 
G \left[ \frac{1 - \exp \left( -\frac{t - L}{T} \right)}{T} \right] & (t \geq L) \\
0 & (t < L)
\end{cases}
\]

where \( G \) is static gain \( \text{[ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}] \), \( L \) is transport delay (s), and \( T \) is time constant (s). Change in R from baseline (6R) in response to the SNP infusion can be expressed similarly and is characterized by \( G \text{[mmHg} \cdot \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}] \), \( L \), and \( T \) (s). We estimated the parameters of the transfer function by approximating \( \delta S_I \) and 6R to Eq. 1 using the least square method. We averaged the parameters of the transfer function of SI response for 10 animals and those of R response for 6 animals. The averaged parameters were used to determine the PI gain constants, \( K_p \) and \( K_i \), 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 6V, we determined the constants (\( X_1, Y_1, X_2, \text{and } Y_2 \)) 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 hemodynamic variables to reach the acceptable ranges of the target values (\( \pm 10 \text{mmHg} \) for AP, \( \pm 10 \text{ml} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \) for CO, \( \pm 2 \text{mmHg} \) 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
Table 1. Hemodynamic data at baseline and after left circumflex coronary artery embolization

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<th>Baseline</th>
<th>Embolization</th>
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<tr>
<td>HR, beats/min</td>
<td>141.3 (19.5)</td>
<td>146.2 (28.8)</td>
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<td></td>
<td>[112.0–188.3]</td>
<td>[81.4–197.9]</td>
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<td>AP, mmHg</td>
<td>109.1 (18.7)</td>
<td>90.9 (16.5)</td>
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<td>[76.4–140.0]</td>
<td>[66.9–135.6]</td>
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<td>COI, ml/min</td>
<td>131.4 (40.9)</td>
<td>66.8 (23.3)</td>
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<td></td>
<td>[64.5–229.2]</td>
<td>[30.3–121.7]</td>
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<tr>
<td>Pla, mmHg</td>
<td>7.5 (1.9)</td>
<td>19.4 (6.2)</td>
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<td></td>
<td>[4.7–12.8]</td>
<td>[7.9–34.5]</td>
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<tr>
<td>Pra, mmHg</td>
<td>4.2 (1.2)</td>
<td>6.0 (1.8)</td>
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<td></td>
<td>[2.1–7.2]</td>
<td>[3.5–9.9]</td>
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<tr>
<td>SL, ml/kg</td>
<td>31.0 (6.6)</td>
<td>32.3 (4.9)</td>
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<td>[21.7–45.2]</td>
<td>[20.6–43.7]</td>
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Values are means (SD) \((n = 35\) in each group). Numbers in brackets are the ranges. HR, heart rate. AP, systemic arterial pressure; COI, cardiac output; Pla, left atrial pressure; Pra, right atrial pressure; SL, 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 SL 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 \(\delta SL\) during Dob infusion \((n = 10)\) and that of \(\delta R\) during SNP infusion \((n = 6)\), respectively. Dob infusion increased \(\delta SL\), and SNP infusion decreased \(\delta R\) exponentially. The results of the fit of \(\delta SL\) and \(\delta R\) 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 \(\delta SL\) and \(\delta R\), suggested that the approximation of \(\delta SL\) and \(\delta R\) 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 \([K_i = 0.01\ s^{-1}, K_p = 0.06\ \mu g\cdot kg^{-1}\cdot min^{-1}\cdot (ml\cdot min^{-1}\cdot kg^{-1})^{-1}]\) and for SNP infusion \([K_i = 0.007\ s^{-1}, K_p = -1.37\ \mu g\cdot kg^{-1}\cdot min^{-1}\cdot (mmHg\cdot min\cdot ml^{-1}\cdot kg^{-1})^{-1}]\).

Figure 3C shows the averaged time course of \(\delta V\) in response to Dex infusion \((n = 5)\). \(\delta V\) increased and plateaued \([7.2\ ml/kg (SD\ 4.3)]\ around 30 min after the cessation of Dex infusion. \(\delta V\) 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 \(\delta V\) after a single intravenous injection of Fur (20 mg, \(n = 7\)). \(\delta V\) 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

\[
\begin{align*}
X_{1} &= 110.22, \quad Y_{1} = 12.18, \\
X_{2} &= 12.57, \quad Y_{2} = 13.45.
\end{align*}
\]

Fig. 3. Response of cardiovascular parameter to drug infusion. A: averaged response of SL to stepwise Dob infusion \((6\ \mu g\cdot kg^{-1}\cdot min^{-1})\) \((n = 10)\). The ordinate indicates change in SL from baseline \((\delta SL)\). B: averaged response of R to stepwise SNP infusion \((2\ \mu g\cdot kg^{-1}\cdot min^{-1})\) \((n = 6)\). The ordinate indicates change in R from baseline \((\delta R)\). C and D: averaged response of V to Dex infusion \((0.4\ ml\cdot min^{-1}\cdot kg^{-1})\) \((C, n = 5)\) and to Fur \((20\ mg)\) injection \((D, n = 7)\). The ordinates indicate change in V from baseline \((\delta V)\). 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),

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<th>G</th>
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<th>T</th>
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<th>SEE</th>
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<tbody>
<tr>
<td>δS_L</td>
<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>δR</td>
<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>
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Values are means (SD). δS_L, change in SL from baseline; δR, change in R from baseline; G, static gain of δS_L [ml·min⁻¹·kg⁻¹·μg·kg⁻¹·min⁻¹] and of δR [mmHg·min·ml⁻¹·kg⁻¹]; L, transport delay (s); T, time constant (s); r, correlation coefficient; SEE, standard error of the estimate of δS_L (ml·min⁻¹·kg⁻¹) and of δR (mmHg·min·ml⁻¹·kg⁻¹).

Fig. 4. Time courses of infusion rates of Dob and SNP, and cumulated volume of infused Dex (A), cardiovascular parameters (B), and hemodynamic variables (C) in 1 representative animal during closed-loop control of hemodynamics. Broken horizontal lines in B indicate target parameters (top, SL*; middle, R*; bottom, V*). Broken horizontal lines in C indicate target hemodynamic variables (top, AP*; middle, CO*; bottom, Pla*). Drug infusion rates were adjusted so that the cardiovascular parameters reached the respective target values. As the parameters got closer to their targets, all 3 hemodynamic variables approached their respective target values.

Table 2. Parameters of step response of SL and R

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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>Before (n = 12)</th>
<th>During (n = 12)</th>
<th>After (n = 11)</th>
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<tr>
<td>HR, beats/mm</td>
<td>147.4 (26.8)</td>
<td>149.4 (25.0)</td>
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<tr>
<td>AP, mmHg</td>
<td>86.7 (22.4)</td>
<td>97.0 (7.4)</td>
</tr>
<tr>
<td>CO, ml·min⁻¹·kg⁻¹</td>
<td>53.7 (14.6)</td>
<td>96.7 (5.3)†</td>
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<tr>
<td>Pla, mmHg</td>
<td>21.8 (5.5)</td>
<td>10.8 (1.2)†</td>
</tr>
<tr>
<td>Ppa, mmHg</td>
<td>6.9 (1.8)</td>
<td>4.4 (0.9)†</td>
</tr>
<tr>
<td>SaO₂, ml·min⁻¹·kg⁻¹</td>
<td>413 (4.0)</td>
<td>327 (2.6)†</td>
</tr>
<tr>
<td>R, mmHg·min·ml⁻¹·kg</td>
<td>1.5 (0.3)</td>
<td>1.0 (0.1)†</td>
</tr>
<tr>
<td>V, ml/kg</td>
<td>34.2 (4.9)</td>
<td>28.5 (2.3)†</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 information 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 S\textsubscript{L} 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. 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 S\textsubscript{L} 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 S\textsubscript{L} 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 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 a major problem because the pathology 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).

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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):

\[ CO = S_R \times [\ln(Pla - 2.03) + 0.80] \]  

(A1)

and CO to Pra (mmHg) as follows:

\[ \text{CO} = \frac{S_L \times [\ln(\text{Pra} - 1.0) + 0.88]}{R} \]  

(A2)

SL and Sa (ml·min⁻¹·kg⁻¹) are parameters representing the preload sensitivity of CO, i.e., the pumping ability of the left and right heart, respectively. These relations are consistent among different animals (24). In a preliminary study, we found that the ratio of SR to SL (\( \alpha \)) remains fairly constant during infusion of dobutamine (data not shown). This suggests that once we know \( \alpha \), we can predict Sa in relation to a known change in SL. Therefore we used SL to parameterize the integrated CO curve. SL can be calculated from CO and Pla by rewriting Eq. A1 as follows:

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

(A3)

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

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

(A4)

\[ \text{V} (\text{ml/kg}) = \text{total stressed blood volume, and COV (ml·min⁻¹·kg⁻¹)} \] 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:

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

(A5)

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

\[ R = (AP - \text{Pra}) / \text{CO} \]  

(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 Sa are calculated to determine \( \alpha \). SR (Sa*) corresponding to SL* is predicted as:

\[ S_R* = \alpha \times S_L* \]  

(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

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