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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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 (ΔSL = SL* − SL) and the difference between R* and R (ΔR = R* − R), proportional-integral (PI) feedback controllers adjust infusion rates of Dob and SNP, respectively (Fig. 2A). In the PI controller (Fig. 2B), ΔSL (or ΔR) 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...
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 (ΔV = 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 ΔV ≥ X, ml/kg then infuse Dex (Y1, ml/min)
Rule 2: If ΔV < X, ml/kg then inject Fur (Y2, mg)

We determined values of X1, Y1, X2, and Y2 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 left and right atrium to measure Pla and Pra, respectively. They were connected to pressure transducers (DX-200, Nihon Kohden). The junction between the vena cavae and the right atrium was taken as the reference point for zero pressure. The undamped natural frequency 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 (CIV-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 μm 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⁻¹·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 μg·kg⁻¹·min⁻¹ for 10 min to obtain a step response of SL. In six dogs, we infused SNP at 2 μg·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⁻¹·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 SL*, V*, and R* (see APPENDIX I). 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(PC)I, 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 SL and R by a transfer function of a first-order model with a transport delay. In this model, change in SL from baseline (δSL) in response to Dob infusion can be expressed by the following formula:

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

where G is static gain [ml·min⁻¹·kg⁻¹·(μg·kg⁻¹·min⁻¹)⁻¹], L is transport delay (s), and T is time constant (s). Change in R from baseline (δR) in response to the SNP infusion can be expressed similarly and is characterized by G [mmHg·ml⁻¹·kg⁻¹·μg⁻¹·min⁻¹]L (s), and T(s). We estimated the parameters of the transfer function by approximating δSL and δR to Eq. 1 using the least square method. We averaged the parameters of the transfer function of SL response for 10 animals and those of R response for 6 animals. The averaged parameters were used to determine the PI gain constants, Kp and Kp, 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 (δV) in response to the infusion of Dex and Fur. On the basis of δV, we determined the constants (X1, Y1, X2, and Y2) of the if-then rules.

Efficacy of the automated drug delivery system. We calculated the following indexes to evaluate the accuracy and stability of 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 (±10 mmHg for AP, ±10 ml·min⁻¹·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
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 ₆'[S] during Dob infusion (n = 10) and that of ₆[R] during SNP infusion (n = 6), respectively. Dob infusion increased ₆[S] and SNP infusion decreased ₆[R] exponentially. The results of the fit of ₆[S] and ₆[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 ₆[S] and ₆[R], suggested that the approximation of ₆[S] and ₆[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 [₆[Kp] = 0.01 s⁻¹, ₆[Ki] = 0.06 µg·kg⁻¹·min⁻¹·(ml·min⁻¹·kg⁻¹)⁻¹] and for SNP infusion [₆[Kp] = 0.007 s⁻¹, ₆[Ki] = −1.37 μg·kg⁻¹·min⁻¹·(mmHg·min·ml⁻¹·kg⁻¹)⁻¹].

Figure 3C shows the averaged time course of ₆[V] in response to Dex infusion (n = 5). ₆[V] increased and plateaued [7.2 ml/kg (SD 6.4)] after the cessation of Dex infusion. ₆[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 ₆[V] after a single intravenous injection of Fur (20 mg, n = 7). ₆[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 ₆[X] = 1 ml/kg, ₆[Y] = 10 ml/min, ₆[Z] = −2 ml/kg, and ₆[W] = 10 mg. To avoid oscillation between hypovole-
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 S₁, R, and V. Infusion rates of Dob, SNP, and Dex were adjusted so that S₁, 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 S₁ and S₁* (S₁ – S₁*), 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. S₁ 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 2. Parameters of step response of S₁ and R

<table>
<thead>
<tr>
<th></th>
<th>G</th>
<th>L</th>
<th>T</th>
<th>r</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>δS₁</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>
</tr>
</tbody>
</table>

Values are means (SD). δS₁, change in S₁ from baseline; δR, change in R from baseline; G, static gain of δS₁ [ml·min⁻¹·kg⁻¹ (μg·kg⁻¹·min⁻¹)]; L, transport delay (s); T, time constant (s); r, correlation coefficient; SEE, standard error of the estimate of δS₁ (ml·min⁻¹·kg⁻¹) and of δR (mmHg·min·ml⁻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).

**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

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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>SV, 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 (5.4)‡</td>
</tr>
</tbody>
</table>

Values are means (SD). *P < 0.05, †P < 0.01 vs. Before; ‡P < 0.01 vs. During.
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 properties 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 in accordance with the vascular conductance (1/resistance) and AP, thereby achieving appropriate response to peripheral metabolic demands and avoiding hemodynamic abnormalities exhibited by other total artificial heart control systems. Their results also suggest that it is essential to consider the mechanical determinant of circulation for the control of the hemodynamic variables.

Our approach is advantageous from the perspective of control engineering. The three drug controllers (Fig. 2A) are designed on the basis of only four input-output relations between the drug infusion and the response of the controlled parameter; namely, Dob-SI, SNP-R, Dex-V, and Fur-V (Fig. 3). We also found that Dob decreases R and increases V, and SNP increases SI and decreases V (data not shown), which are compatible with previous studies (7, 22, 23). If these secondary effects induce significant interactions among the three closed loops, additional controllers would be needed to compensate for the interactions (4). However, our results indicate that these secondary effects are small enough to be compensated by the three drug controllers, and additional controllers are not necessary. The fact that the three closed loops are effectively decoupled drastically simplifies the entire system. This also permits system operators to understand its behavior easily (4).

Although we fix the PI gain constants and the constants of if-then rules, controls of cardiovascular parameters are accurate and stable (Fig. 4B). There are interindividual differences in the response of the parameters to drug infusion (Fig. 3). There should also be intrapatient differences in the response over time. However, our results indicate that the three drug controllers effectively compensate for all of these differences and do not require adaptive tuning in individual animals as in the previous system. As long as each cardiovascular parameter responds sensitively to the corresponding agent, our system is able to achieve target values for all the parameters, thereby achieving target hemodynamic variables.

Our system explicitly quantifies cardiac pump function, preload, and afterload, thereby controlling the overall hemodynamics. We believe that this unique feature of our system is intuitively appealing and is acceptable to clinicians.

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 SI 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 SI 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 Sr was accurate and stable. However, it would be impossible to restore Sl pharmacologically if Sr 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 Sr 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 Sr, 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):

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

(A1)

and CO to Pra (mmHg) as follows:

\[
CO = S_r \times [\ln(Pra - 1.0) + 0.88]
\]

(A2)

Sr 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 (α) remains fairly constant during infusion of dobutamine (data not shown). This suggests that once we know α, we can predict Sa in relation to a known change in Sr. Therefore we used Sr to parameterize the integrated CO curve. Sr can be calculated from CO and Pla by rewriting Eq. A1 as follows:

\[
S_l = CO/[\ln(Pla - 2.03) + 0.80]
\]

(A3)

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

\[
V = V/0.129 - 19.61Pra - 3.49Pla
\]

(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:

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

(A5)

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

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

(A6)

APPENDIX B

Determination of Target Parameters

On the basis of AP*, CO*, and Pla*, our system determines Sl*, V*, and R* as follows: S* 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 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:

\[
Pra^* = \exp([CO^*]/(S_l^*) - 0.88) + 1.0
\]

(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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