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Automated drug delivery system for the management of hemodynamics and cardiac energetic in acute heart failure

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Abstract— **We have developed a novel automated drug delivery system for simultaneous control of systemic arterial pressure (AP), cardiac output (CO), and left atrial pressure (P_{LA}) in acute heart failure. The circulatory equilibrium framework we established previously discloses that AP, CO, and P_{LA} are determined by equilibrium of the mechanical properties of the circulation, i.e. pumping ability of the left heart, stressed blood volume and systemic arterial resistance. Our system directly controls the three mechanical properties with cardiovascular drugs including inotropes and vasodilators, thereby controlling AP, CO, and P_{LA}. Furthermore, by precisely controlling bradycardia and LV inotropy, our system enables to improve cardiac energetic efficiency while preserving AP, CO, and P_{LA} within acceptable ranges. In conclusion, by directly controlling the mechanical properties of the heart and vessel, our automated system realizes comprehensive management of hemodynamics in acute heart failure.**

I. Introduction

In the management of patients with acute heart failure after myocardial infarction or following cardiac surgery, cardiovascular agents such as inotropes and/or vasodilators are commonly used to control systemic arterial pressure (AP), cardiac output (CO) and left atrial pressure (P_{LA}). Since 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.

Although several closed-loop systems [1, 2] to automate drug infusion have been developed to facilitate this process, no closed-loop system so far developed is capable of controlling the overall hemodynamics; i.e., controlling AP, CO and P_{LA} simultaneously. This is because all previous systems attempted to directly control AP and CO by estimating response of the variable to drug infusion [1, 2]. This approach is inapplicable because of the difficulties to estimate simultaneous AP, CO and P_{LA} responses to the infusion of multiple drugs.

In this study, we developed a new automated drug delivery system to control AP, CO and P_{LA} [3]. To overcome the difficulty of the previous systems, our system adopted a strikingly original approach. We previously developed a circulatory equilibrium framework by extending the Guyton's classic framework [4]. 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 [5-7]. The intersection point of the integrated CO curve and the venous return surface predicts the equilibrium point of CO, P_{LA} and right atrial pressure (P_{RA}) (Fig. 1). Once CO, P_{LA} and P_{RA} are predicted from the intersection point, systemic arterial resistance determines AP. Based on this framework, instead of directly controlling AP, CO, and P_{LA}, 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 AP, CO and P_{LA}. The purpose of this study was, therefore, to develop and validate the automated drug delivery system.

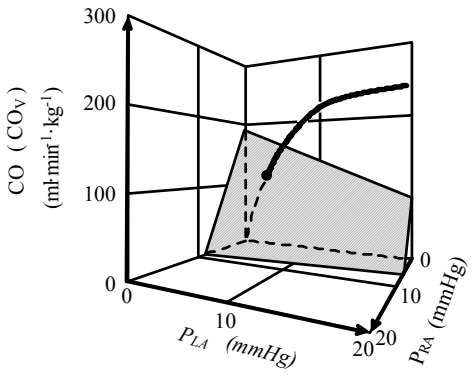

Fig. 1. Diagram of circulatory equilibrium for CO, venous return (CO_V), P_{LA}, and P_{RA}. The equilibrium CO, P_{LA} and P_{RA} are obtained as the intersection point of the venous return surface and integrated cardiac output curve.

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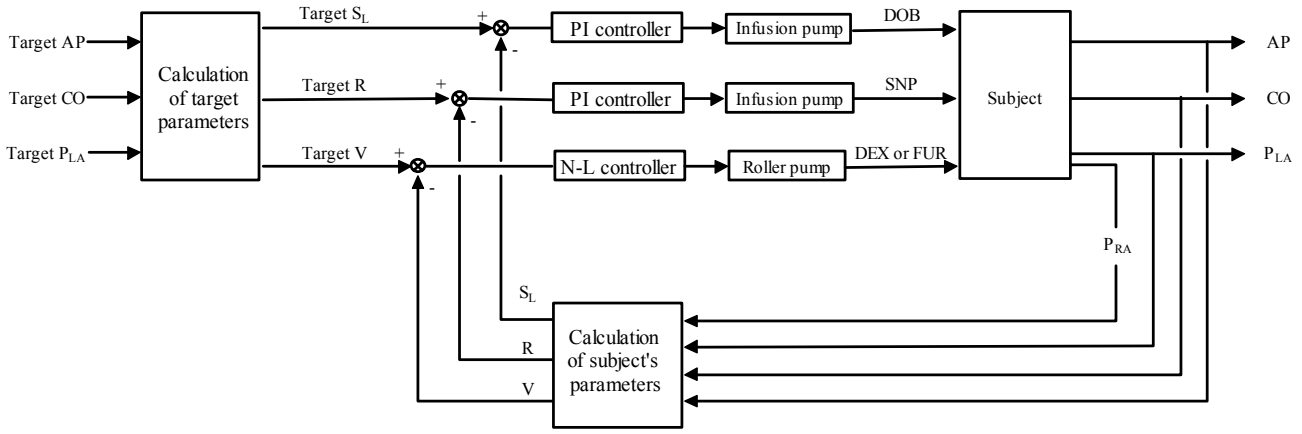

Fig. 2. Schematic illustration of an automated drug delivery system for simultaneous control of AP, CO and P_{LA}. Proportional-integral (PI) feedback controllers adjust infusion rate of DOB and SNP to minimize the difference between target and subject's S_L and those of R, respectively. Nonlinear (N-L) feedback controller adjusts infusion of DEX or injection of FUR to minimize the difference between target and subject's V.

In acute heart failure, cardiac energetic efficiency should also be improved. Theoretically, if heart rate (HR) is reduced while AP, CO and P_{LA} are maintained by preserving S_L with precisely increased LV contractility, it is possible to improve cardiac energetic efficiency and reduce LV oxygen consumption per minute (MVO_2) [8]. In the present study, we also investigated whether this hemodynamics can be accomplished in acute heart failure using our automated drug delivery system.

II. Methods

A. Automated drug delivery system

The integrated CO curve is parameterized by the pumping ability of the left heart (S_L) [ml·min^{-1}·kg^{-1}], the venous return surface by total stressed blood volume (V) [ml·kg^{-1}], and the systemic arterial resistance by R [mmHg·ml^{-1}·min·kg], which are calculated for a given set of AP, CO, P_{LA} and P_{RA} as the following formulas [3];

$$S_L = CO/[\ln(P_{LA} - 2.03) + 0.8] \quad (1)$$

$$V = (CO + 19.61P_{RA} + 3.49P_{LA}) \times 0.129 \quad (2)$$

$$R = (AP - P_{RA})/CO \quad (3)$$

Fig. 2 is a schematic illustration of the automated drug delivery system [3]. Once target values for AP, CO and P_{LA} are defined and fed into the computer, it calculates the target values for S_L, R, and V using Equations (1)-(3). The subject's S_L, R, and V are calculated from measured AP, CO and P_{LA} values using Equations (1)-(3). To minimize the differences between target and subject's S_L and R, proportional-integral feedback controllers adjust the infusion rates of DOB and SNP, respectively. To minimize the difference between target and subject's V, a nonlinear feedback controller adjusts the infusion of DEX or injection of FUR. Gain and rules of the controllers were predefined on the basis of the step responses of S_L, R, and V to the infusions of the drugs [3].

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

B. Animal experiments to validate performance of the automated drug delivery system

In 12 anesthetized dogs, we acutely created ischemic heart failure by coronary embolization, which decreased CO from 133 ± 42 to 69 ± 22 ml·min^{-1}·kg^{-1}, AP from 109 ± 18 to 91 ± 17 mmHg and increased P_{LA} from 7 ± 2 to 19 ± 6 mmHg.

We connected the animals to the system, and defined target AP (90-105 mmHg), target CO (90-100 ml·min^{-1}·kg^{-1}) and target P_{LA} (8-12 mmHg), which were fed into the system to determine target values for S_L, R, and V as described above. The controllers were then activated by closing the loops. We observed the performance of the system over 50-60 min.

C. Circulatory equilibrium and cardiac energetics

S_L is theoretically related with LV end-systolic elastance (E_{es}, an index of LV contractility), HR, R and diastolic myocardial stiffness (k) as the following formula [7]

$$S_L = \frac{1}{k} \cdot \frac{E_{es}}{(E_{es}/HR) + R} \quad (4)$$

LV Stroke work (SW) is expressed as

$$SW = (AP - P_{LA}) \cdot CO/HR \quad (5)$$

LV pressure-volume area (PVA, an index of total mechanical energy of LV contraction) can be expressed as

$$PVA = AP \cdot AP/2E_{es} + SW \quad (6)$$

LV oxygen consumption per beat (BVO_2) is related to PVA and E_{es} as follows

$$BVO_2 = \alpha \cdot PVA + \beta \cdot E_{es} + \gamma \quad (7)$$

where α, β, and γ are constants. LV mechanical efficiency (ME) and oxygen consumption per minute (MVO_2) are expressed as follows:

$$ME = SW/BVO_2 \quad (8)$$

$$MVO_2 = BVO_2 \cdot HR \quad (9)$$

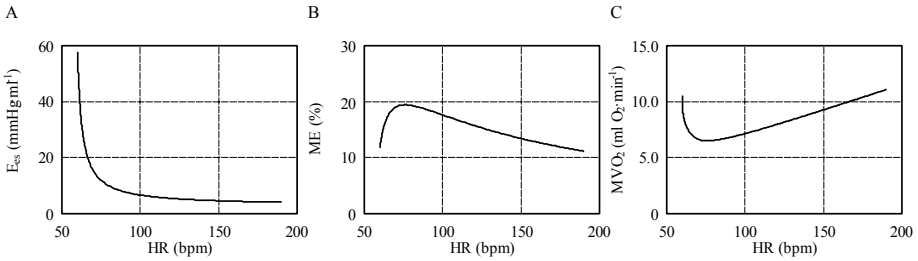

Fig. 3. Simulated relations of heart rate (HR) with left ventricular end-systolic elastance (E_{es}) (**A**), left ventricular mechanical efficiency (ME) (**B**), and left ventricular oxygen consumption per minute (MVO_2) (**C**), when AP, CO and P_{LA} are kept at fixed values.

Using Equations (4)-(9) and fixed values of AP (100 mmHg), CO (100 ml·min^{-1}·kg^{-1}) and P_{LA} (10 mmHg), we numerically simulated the individual relations of HR with E_{es}, ME and MVO_2 (Fig. 3). In these computations, representative k, α, β and γ values (not shown) were used, which are appropriate for a 20-kg dog.

As indicated in Fig. 3, HR is inversely related to E_{es} (Fig. 3A). Over the physiological range of HR for dogs (>80 bpm), ME increases as HR is reduced (Fig. 3B), i.e. cardiac energetic efficiency is optimized. At HR of 75 bpm, ME becomes maximal and MVO_2 becomes minimal (Fig. 3B, C). When HR is reduced from 150 to 110 bpm, E_{es} increases from 4.6 to 5.9 mmHg·ml^{-1} (29% increase) and ME increases from 13 % to 17 % (24 % increase), whereas MVO_2 decreases from 8.9 to 7.2 ml O_2·min^{-1} (19% reduction) [8]. This indicates that as long as HR is within the physiological range, HR reduction together with compensatory LV inotropy (an increase of E_{es}) consistently improves cardiac energetic efficiency and reduces MVO_2.

D. Animal experiments to optimize cardiac energetics using the automated drug delivery system

In 7 anesthetized dogs, we acutely created ischemic heart failure by coronary embolization, which decreased CO from 101±5 to 62±13 ml·min^{-1}·kg^{-1}, AP from 114±4 to 97±14 mmHg and increased P_{LA} from 9 ± 1 to 17±2 mmHg. Zatebradine (0.5 mg·kg^{-1}) was administered intravenously to suppress the intrinsic atrial beat, and atrial pacing was then initiated to control HR (146±8 bpm). After induction of acute heart failure, cardiac energetics were evaluated (*AHF*).

We activated the system with target values of 90-100 mmHg for AP, 80-100 ml/kg/min for CO and 10-12 mmHg for P_{LA}. The system restored AP, CO and P_{LA} to their respective target values within 30 min. After confirming stable hemodynamics, cardiac energetics were evaluated (*Initial HR*). We then reduced the pacing rate in steps of 10 or 20 bpm. The maximum HR reduction (*Lowest HR*) averaged 39±12 bpm. For each HR step, we waited for hemodynamic stabilization, and the measurements of cardiac energetics were performed.

III. Results

A. Performance of the automated drug delivery system

Fig. 4 shows the experimental trial in a representative animal. The system was activated at 0 min. Fig. 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. Fig. 4B shows the time courses of S_L, R and V. Infusion rates of DOB, SNP, and DEX were adjusted so that S_L, R and V reached their respective target values. By controlling the cardiovascular parameters, the automated system controlled AP, CO and P_{LA} accurately and stably as demonstrated in Fig. 4C. AP, CO and P_{LA} reached their respective target levels within 30 min and remained at these levels.

In 12 animals, the average times for AP, CO and P_{LA} to reach the acceptable ranges (± 10 mmHg of target AP, ± 10 ml·min^{-1}·kg^{-1} of target CO, ± 2 mmHg of target P_{LA}) were 5.2 ± 6.6 min, 6.8 ± 4.6min, and 11.7 ± 9.8 min, respectively. The average standard deviations from the target values were small for AP [4.4 ± 2.6mmHg], CO [5.4 ± 2.4ml·min^{-1}·kg^{-1}] and P_{LA} [0.8 ± 0.6 mmHg].

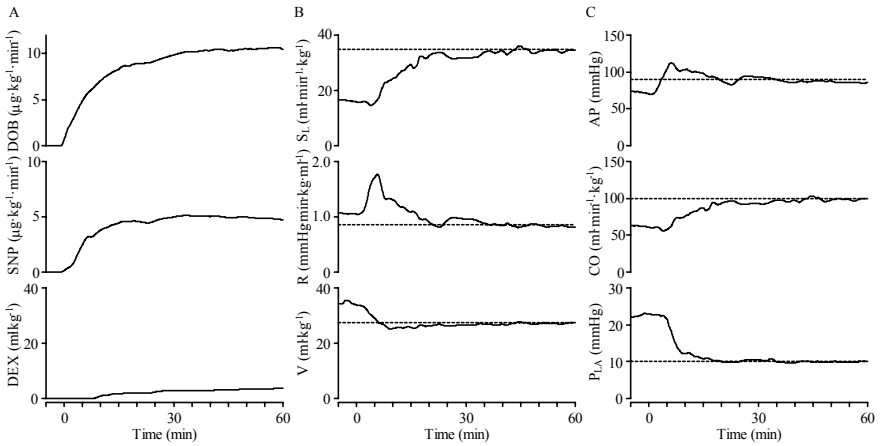

Fig. 4. Time courses of infusion rates of DOB and SNP, and cumulated volume of infused DEX (**A**), cardiovascular parameters (**B**), and hemodynamic variables (**C**) in one representative animal during closed-loop control of hemodynamics. Broken horizontal lines in panel B and C indicate target values.

B. Cardiac energetics improved following bradycardia while preserving normal hemodynamics in heart failure

In seven anesthetized dogs with acute heart failure, the automated drug delivery system restored and maintained normal hemodynamics (CO; 88±3 ml·min^{-1}·kg^{-1}, P_{LA};

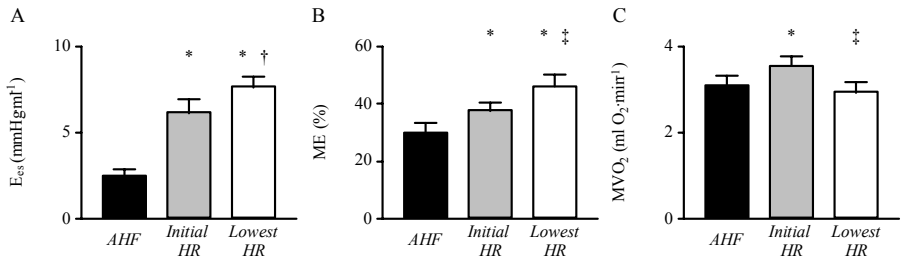

Fig. 5. Cardiac energetics after coronary artery embolization (*AHF*), at the initial HR (*Initial HR*), and at the lowest HR (*Lowest HR*). E_{es}, left ventricular (LV) end-systolic elastance; ME, LV mechanical efficiency; MVO_2, LV oxygen consumption per minute. Data are means ± SEM. *: P<0.01 vs *AHF*. †: P <0.05, ‡: P<0.01 versus *Initial HR*.

10.9±0.4 mmHg), even when zatebradine significantly reduced HR (107±7 bpm, -27±3%).

Fig. 5 summarizes cardiac energetics at *AHF*, *Initial HR*, and *Lowest HR*. When the data at *Initial HR* and *Lowest HR* were compared with those at *AHF*, E_{es} and ME increased significantly. MVO_2 at *Initial HR* also increased compared to that at *AHF*, although MVO_2 at *Lowest HR* was almost identical to that at *AHF*. The automated drug delivery system restored normal hemodynamics with increased energy cost at *Initial HR*, but with diminished energy cost at *Lowest HR*. Comparing the data at *Lowest HR* with those at *Initial HR*, E_{es} increased (+34±14 %), ME increased (+22±6 %) and MVO_2 decreased significantly (-17±4 %). Changes in the LV mechanoenergetic data following HR reduction averaged over seven animals are compatible with those predicted theoretically (Fig. 3).

IV. Discussion

A. Characteristics of our system

Our system controls the mechanical determinants of circulation, and as a result achieves target values for hemodynamic variables [3]. Previous systems attempted to control hemodynamic variables by estimating the apparent input–output relations between drug infusion and response of the controlled variables. In the systems that control AP and CO, all possible input–output relations have to be estimated; namely, inotrope–AP, inotrope–CO, vasodilator–AP, and vasodilator–CO relations [2]. The reason is that these drugs affect AP and CO simultaneously to almost the same degree. If this previous approach is applied to simultaneous control of AP, CO and P_{LA}, at least 9 input–output relations have to be estimated, since at least 3 drugs are required to independently control the three variables. This would make the system extremely complicated, and therefore be practically unfeasible. The three drug controllers in our system (Fig. 2) are designed on the basis of only three input–output relations between drug infusion and response of the controlled parameter; namely, DOB–S_L, SNP–R and DEX/FUR–V. The fact that the three closed loops are effectively decoupled simplifies the entire system. This also permits a system operator, who would be a physician untrained in control engineering, to understand its behavior easily

B. Simultaneous optimization of cardiac energetic and hemodynamics

The degree of reduction in MVO_2 (17 %, *Lowest HR* vs *Initial HR* in Fig. 5C) when HR was reduced by 30% in the present experiment is less than that observed in beta-blockade treatment. For example, atenolol decreased MVO_2 by 40% when HR was reduced by 30% in dogs during exercise. Negative ventricular inotropy accompanying HR reduction accounts for the further reduction in MVO_2 achieved by beta-blockade. However, in acute heart failure, use of beta-blockers is contraindicated owing to its adverse effects on systemic hemodynamics. Taken together, the degree of reduction in MVO_2 obtained in this study is reasonable considering that it is achieved without sacrificing the normal hemodynamic condition.

V. Conclusion

By directly controlling the mechanical properties of the heart and vessel, our automated system enables comprehensive management of hemodynamics in acute heart failure.

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